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THE WESTERN Journal of Medicine

VOLUME 129 • JULY 1978

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Warnings: Safety during pregnancy has not been established. Sulfonamides should not be used for group A beta-hemolytic streptococcal infections and will not eradicate or prevent sequelae (rheumatic fever, glomerulonephritis) of such infections. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported and early clinical signs (sore throat, fever, pallor, purpura or jaundice) may indicate serious blood disorders. Frequent CBC and urinalysis with microscopic examination are recommended during sulfonamide therapy. Insufficient data on children under six with chronic renal disease.
Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy, bronchial asthma; in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.
Adverse Reactions: *Blood dyscrasias* (agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia); *allergic reactions* (erythema multiforme, skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis); *gastrointestinal reactions* (nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis and stomatitis); *CNS reactions* (headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia); *miscellaneous reactions* (drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon). Due to certain chemical similarities with some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia as well as thyroid malignancies in rats following long-term administration. Cross-sensitivity with these agents may exist.
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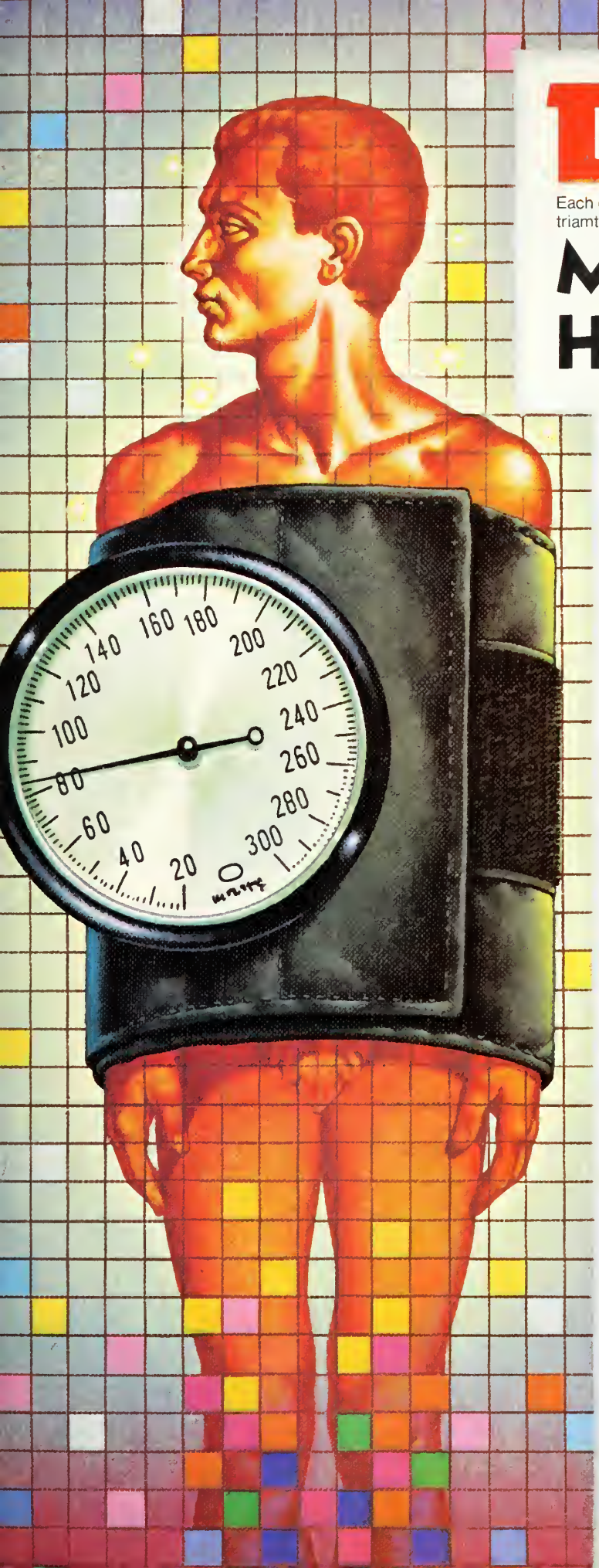

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Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K+ frequently; both can cause K+ retention and elevated serum K+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine

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PRECAUTIONS: As with other antibacterial preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs.

ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Ototoxicity and nephrotoxicity have been reported (see Warning section).

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1954
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Indications: Oral potassium therapy for the prevention and treatment of hypokalemia which may occur secondary to diuretic or corticosteroid administration. May be used in the treatment of cardiac arrhythmias due to digitalis intoxication.

Contraindications: Severe renal impairment with oliguria or azotemia, untreated Addison's disease, adynamia episodica hereditaria, acute dehydration, heat cramps and hyperkalemia from any cause.

Precautions: Potassium intoxication by oral administration rarely occurs in patients with normal kidney function, however, potassium supplements must be administered with caution, since the amount of the deficiency or daily dosage is not accurately known. Frequent checks of the clinical status of the patient, and periodic ECG and/or serum potassium levels should be made. High serum concentrations of potassium ion may cause death through cardiac depression, arrhythmias or arrest. This drug should be used with caution in the presence of cardiac disease.

In hypokalemic states, especially in patients on a low-salt diet, hypochloremic alkalosis is a possibility that may require chloride as well as potassium supplementation.

Adverse Reactions: Nausea, vomiting, diarrhea, and abdominal discomfort have been reported. The most severe adverse effect is hyperkalemia.

Overdosage: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications". Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours.

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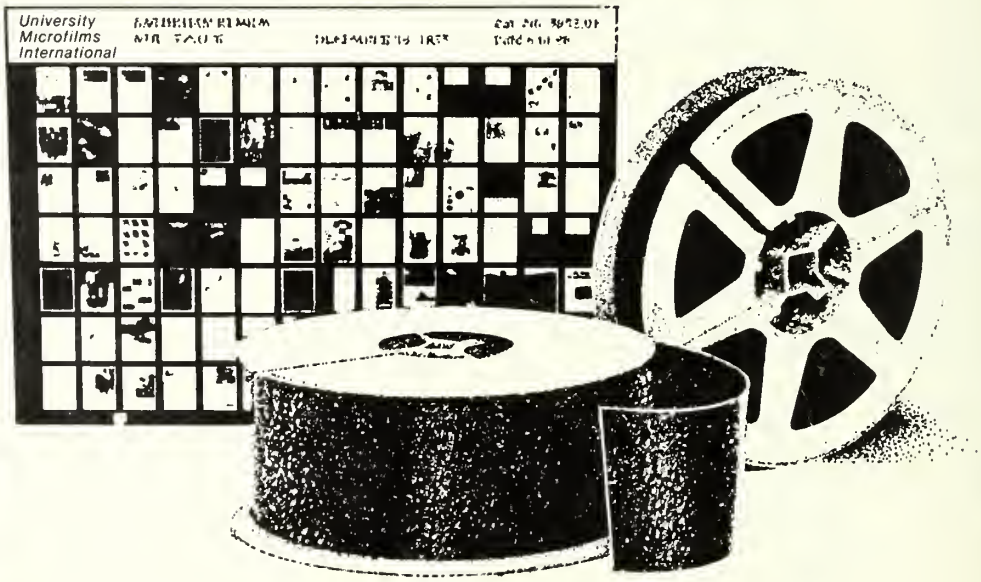

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Alcoholism

Earlier Diagnosis and Definition of the Problem

DONALD E. GIRARD, MD, *and* BRUCE E. CARLTON, MD, *Portland, Oregon*

There are important measurements of alcoholism that are poorly understood by physicians. Professional attitudes toward alcoholic patients are often counterproductive. Americans spend about $30 billion on alcohol a year and most adults drink alcohol. Even though traditional criteria allow for recognition of the disease, diagnosis is often made late in the natural course, when intervention fails. Alcoholism is a major health problem and accounts for 10 percent of total health care costs. Still, this country's 10 million adult alcoholics come from a pool of heavy drinkers with well defined demographic characteristics. These social, cultural and familial traits, along with subtle signs of addiction, allow for earlier diagnosis. Although these factors alone do not establish a diagnosis of alcoholism, they should alert a physician that significant disease may be imminent. Focus must be directed to these aspects of alcoholism if containment of the problem is expected.

ALTHOUGH THE medical complications of alcoholism are familiar to most practicing physicians, there remain aspects of the disorder that are poorly understood by the profession. This understanding is critical if containment is a goal. The prevalence of alcoholism, its influence on mortality rates and its economic impact are startling but they generate little medical interest. Despite the development of diagnostic criteria, the disorder is often identified late in the natural course when end-stage disease allows little therapeutic intervention. Still there are clues to the earlier diagnosis of alcoholism in demographic information, in well-documented social, cultural and familial characteristics, and in early signs of addiction. Unfortunately these data are infrequently utilized and reflect physician attitudes toward alcoholism that are often counterproductive.

If the medical profession is to deal with alcoholism effectively it must consider the diagnosis in the early stages of habituation. The physician force must focus on earlier clues. It must search for social, familial and cultural attitudes that support the diagnosis, and ask questions which

From the Ambulatory Care Section and Medicine Service, Veterans Administration Hospital, Portland, and Division of General Medicine, Department of Medicine, University of Oregon Health Sciences Center.

Submitted October 25, 1977.

Reprint requests to: Donald E. Girard, MD, ACOS for Ambulatory Care, Veterans Administration Hospital (648/11C), Sam Jackson Park, Portland, OR 97207.

will uncover the early historical danger signals of alcoholism. Finally, a change in physician attitudes toward this treatable disease is required through an understanding of the disorder and avoidance of a pejorative approach.

Attitudes Toward Alcoholism

Alcoholism has not traditionally been a venerable disease state. In the second edition of his *Modern Practice of Physic,* in 1762, John Ball summarized alcohol-related disorders in a single paragraph from a chapter entitled, "Of Madness and Melancholy."[1] More than 100 years later William Osler included a short discussion on alcoholism in the chapter "Intoxications, Sunstroke and Obesity" in his newly published *Practice of Medicine.*[2]

Riley and Marden interviewed a large group of general practitioners in 1945 to find that while most treated alcoholic patients, almost all felt that they afforded their patients little more than temporary relief.[3] Similar attitudes were identified among Jackson, Mississippi, physicians several years later.[4] Typically, these physicians regarded alcoholic patients as "lacking motivation toward health," "unwilling to assume responsibility" and "depriving other patients of care by consuming therapist time."

Professional attitudes have changed little to the present. Recently MacDonald and Patel, in reviewing attitudes in Scottish hospitals, found that among all of the organic and psychiatric illness, physicians least liked to treat alcoholism.[5] This attitude appears to be well established early in professional life. It has been reported that graduating physicians are more cynical and less humanitarian than when they entered medical school and that, among first-year and second-year medical students, interns and residents, feelings toward alcoholic patients deteriorate directly with time.[6,7]

Physician attitudes toward alcoholics have complicated origins. Notable discussants stress the profession's innate attitudes of independence, autonomy, self-control and self-reliance, reflections of middle class puritan ethics, to explain intolerance toward management of alcoholic patients. Lisansky points to both conscious and subconscious concepts which act as deterrents to physicians in their therapeutic attempts.[8] Among them he includes: lack of knowledge about alcoholism; confusion with its "disease" status; anger at the alcoholic who is felt to be willful, uncooperative and unmodifiable; bad family experiences with alcoholics; the fear of losing a patient who is informed of his alcoholic status; and misgivings about one's own drinking patterns.

Robert Sparks, while corroborating Lisansky's observations, adds lay misconceptions as a force adversely affecting physician attitudes; that is, the belief that a single factor is responsible for alcoholism; the reluctance to admit that a close friend or relative has a drinking problem; one's own inability to control his drinking; the stereotypic alcoholic as the skid row resident; the persistent social pressure for everyone to drink; the ever present tendency to admire the person who can "hold his liquor" and who is the "life of the party," and the constant depiction by advertising media of alcohol drinking as a sign of appropriate sophistication.[9]

Lastly, medical school curricula have devoted almost no time to alcoholism. This lack of focus on the problem tacitly condones the absence of understanding, interest and involvement and allows the unknowledgeable physician to be a target for the disease.

Magnitude of the Alcoholism Problem

Unfortunately, alcoholism represents one of the nation's most serious public health problems. Alcohol overuse generates cost to society within several contexts: lost production, health care, motor vehicle accidents, fire, crime, and certain social programs created to defend against alcohol abuse (highway safety, fire protection, criminal justice and the like).[10]

In 1950 Americans were spending $8 billion a year on alcohol. Government agencies collected $3.2 billion in alcohol taxes, but allocated virtually nothing to anti-alcoholism programs.[11] By 1976 some $30 billion was spent on alcohol and $9 billion collected in taxes.[11] Overall, the federal government allocates approximately 6¢ to alcohol programs for every dollar it receives in revenue. In addition, the alcohol industry represents a major power in this country's economic structure. While total annual subsidy for federal alcohol program spending is just over $300 million, the same amount is allocated annually by the liquor industry for advertising. The advertising media have been very successful over the past 20 years. The per capita consumption of beer has increased by 22 percent, of hard liquor by 56 percent and of wine by 80 percent.[11] A total of 71 percent of adult Americans drink alcoholic beverages, the largest percentage ever.[12] The *Second Special*

Report to Congress on Alcohol and Health showed that average per capita annual alcohol consumption is 2.63 gallons of absolute alcohol (2.16 gallons of wine, 2.60 gallons of distilled spirits and 26.6 gallons of beer).[13]

According to the figures developed under the auspices of the National Institute on Alcohol Abuse and Alcoholism, the total cost of alcohol abuse in the United States in 1971 was approximately $31.4 billion. With current inflationary trends, that represents a figure of $43.4 billion.[10] Health care costs attributable to alcohol overuse in 1971 were estimated at approximately 10 percent of total health care costs.[10] Of these expenses, most are allocated to direct hospital care. The enormous impact of alcoholism is reflected in data on patients admitted to hospital.

Alcohol abuse is an important reason for hospital admission and a major contributor to mortality in our hospitals. A review of the records of 200 most recently discharged patients from the medical service of the Portland Veterans Administration and University Hospital of the University of Oregon Health Sciences Center has shown alcoholism to be a definable medical problem in 26 percent and 20 percent of all patients, respectively. Of these cases of alcoholism, 75 percent fulfilled classic criteria of the National Council on Alcoholism. Of the alcoholic patients in the review, more than half from each hospital had been admitted as a direct result of alcohol abuse. Further, alcoholism or its sequelae complicated the hospital courses in almost a third of these cases. One of every five of the patients died in the hospital. Arrangements for follow-up for alcoholism were made for only 5 percent of the survivors.

Death rates from alcohol abuse in age groups at major risk are more than twice those for the general population. While more consistent data have been recovered from studies of persons admitted to hospitals for alcohol treatment, two problems inherent in these studies have made them inaccurate. A large segment of the alcoholic population is not included and the sickest patients are preferentially admitted to hospital.[13] Still in a Swedish study where all persons reported for drinking problems were included whether admitted to hospital or not, mortality rates were 20 percent higher than in the general population for all age groups.[14]

Identifying Heavy Drinkers

Roughly 10 million adults in this country are alcoholic.[15,16] Of the adult population who consume alcohol, about 18 percent (20 percent of men and 8 percent of women) drink heavily; that is, almost daily and in sufficient quantities to be intoxicated several times a month. It is from this pool of heavy drinkers that the alcoholic population emerges.[16]

Because the alcoholic population evolves from heavy and problem drinkers, identifying characteristics of these groups is important. Demographic information supplies such data. Inhabitants of the South-Central United States consume the least alcohol, while those in New England and the Pacific regions consume the most.[13] More than 70 percent of the American adult population drink alcohol, and progressively younger age groups are involved. Between 71 and 92 percent of high school youths have at least tried alcohol and 14 percent of male high school seniors overdose with alcohol at least once a week.[11,17,18] Young men (18 to 20 years old and 35 to 39 years old) and young women (21 to 29 years old) consume the highest proportions of alcohol.[13] Alcohol consumption is lowest among groups whose cultural demands discourage or contraindicate alcohol overuse. For example, Jews and Italian-Americans are at small risk, while Irish-Americans and American Indians are at great risk. Although religious affiliation no longer strongly influences alcohol consumption, Catholics and liberal Protestants average highest alcohol intake and conservative Protestants and Jews the least. The highest percentage of abstainers comes from the least educated groups and the greatest proportion of heavy drinkers from groups with graduate educations. Likewise, more persons from low socioeconomic status are abstainers, and drinking practices increase with social status. Paradoxically, drinking problems seem to evolve more frequently per person at risk from lower socioeconomic populations. Heavy alcohol consumption is greatest among separated, then divorced and then single persons, and least among married persons. Farm owners have the lowest number of alcohol problems among persons with occupations, while professionals and businessmen have high rates, and semiprofessionals the highest. Both military officers and enlisted men drink more than their civilian peers. Although place of residence plays a less important role than it has traditionally,

persons in urban populations, especially those entering from rural areas, are heavier drinkers. Contexts of drinking may also represent a risk factor. Drinking alone and drinking in bars and taverns, especially alone, result in heavier drinking practices.

If these demographic data are compiled, a stereotypic person at high risk for alcoholism emerges: A young man or woman arising out of socioeconomic depression, educated, professional or semiprofessional, recently separated, who has moved from rural to urban residence and who is an Irish-American Catholic or liberal Protestant, and who is in the military service and resides on the east or west coast. Such a person does not match preconceptions by lay persons of the average alcoholic, the skid row resident.

Social attitudes are important in predisposition to heavy drinking and alcoholism, and many reflect the plentiful use of denial. Cahalan found significant, heavy drinking and alcoholism among persons who answered favorably questions reflecting the social utility of alcohol drinking, and who enjoyed "getting drunk once in a while," and who felt that "drinking is not harmful."[18] Other investigators have shown that heavy drinkers and alcoholics are, in general, not knowledgeable about the effects of alcohol and are unwilling to acknowledge that alcohol is a drug.

Physicians, unfortunately, are at high risk for alcoholism.[19-21] Blachly reported that drugs or alcohol abuse were important factors in 40 percent of violent deaths of physicians between May 1965 and November 1967.[22] From 1961 through 1972, in Oregon, 2.3 percent of physicians were brought before disciplinary boards for alcoholism.[23] Glatt reported the incidence of alcoholic cirrhosis from England's Registrar General's Office in physicians to be 3.5 times that in the general population.[24] Between 3 and 4 percent of alcoholic patients at two large English alcoholic units were physicians, a rate considerably higher than expected.[25] Murray, in a review of data from the Scottish hospitals and Research Intelligence Unit, reported that the incidence of alcoholism for which hospital admission was required was 2.7 times higher for male physicians than social and economic equals.[26] In addition, alcoholism accounted for more than half of all psychiatric hospital admissions for physicians between ages 45 and 54 during the ten-year period studied.

The characteristics of alcoholic physicians are interesting. Bissel and Jones recently compiled data on 98 recovered alcoholic physicians.[27] Psychiatry was the only specialty that had a prevalence greater than expected. A larger than anticipated percentage reported high standing in medical school classes. All but 22 patients had sought professional help, yet more than a third were told by therapists that alcoholism was not the problem. The social and professional sequelae experienced by this group are of interest. More than half reported no obvious change in work status or only admonishment by colleagues. Some 20 percent were warned by a medical society or a licensing board, and a similar number lost hospital privileges. Only 10 percent lost their medical licenses, and a third were not sanctioned at all.

Finally, the question of the role of hereditary and genetic risk factors for alcoholism has been the subject of continuing debate since Ann Roe's report in 1945.[28] In that study she maintained that environmental experience was the only appreciable influence on the development of alcoholism (the nurture hypothesis). Her conclusion was based on the fact that in children of alcoholic parents, removed from their homes at early ages, there developed no appreciable incidence of alcoholism in adulthood. However, the Danish-American studies by Goodwin, Guze and Winokun showed striking genetic predisposition.[15,29] Goodwin designed this study because it allowed utilization of a unique Danish record-keeping system that included a known pool of 15,000 adoptees, separated from biologic parents and raised by nonrelatives. In all, 55 persons were interviewed. All had one biologic parent who had been admitted to hospital for alcoholism and each had been removed from his parents during the first six weeks of life to be raised by nonrelatives. There was no subsequent contact with parents. Similarly, an age-matched control group without alcohol history was studied. The incidence of alcoholism in the offspring with an alcoholic parent was four times that in the other group, and there was no evidence of underlying psychiatric disorder. Subsequent studies showed that the incidence of alcoholism was just as great whether raised by natural parents or not, as long as there was one alcoholic parent (the nature hypothesis).[30]

Last, the influence of familial risk factors on alcoholism has been strengthened by other notable investigations.[31-35] The work of Amark and Winokur showed increased rates of alcoholism among

first-degree family members of alcoholics. The twin studies of Kaij showed similar patterns of alcohol consumption between alcoholic twins and their siblings. The separation studies with half siblings of alcoholics of Shuckit, Goodwin and Winokur showed a correlation between having an alcoholic biologic parent and being an alcoholic. The more recent observations of Winokur showed that alcoholism occurs statistically more frequently among men in families whose women members have high incidences of hereditary recurrent depression.

Toward the Earlier Diagnosis of Alcoholism

In 1945 Jellinek succeeded in developing historical criteria for the diagnosis of alcoholism.[36] Though imperfect and based on a confusing data base, they provided a diagnostic framework not previously available. The National Council on Alcoholism recently published more comprehensive and accurately derived criteria which included three diagnostic levels: classic, providing definite diagnosis; probable, suggesting the diagnosis; and potential, allowing for it.[37] They were developed from physiologic, clinical and behavioral characteristics of alcoholics. In addition, other investigators have focused on early clues, some of which are included by the National Council.[38-41] None of these clues makes a diagnosis of alcoholism certain. Yet each is a warning sign—a danger signal that alcoholism may be operative. In general these clues are historical, and manifestations of four conditions of alcohol addiction: loss of control, craving, tolerance and physical dependence.

Loss of control reflects one's inability to regulate alcohol intake. It may not be detectable in any but the person's own environment, and forces an individual to seek innovative opportunities for drinking; only some of which may be inappropriate. He begins to drink alcohol in the same pattern whether it is a work day, weekend or holiday. The more advanced the stage, the more stereotypic the pattern. Loss of control over consumption makes automobile accidents more likely, forces the person to change employment to jobs that make drinking easier to continue and makes him repeatedly attempt abstinence.

Craving alcohol reflects the subjective compulsion to drink. The patient understands drink-seeking behavior and gives priority to maintaining alcohol intake. He begins to shift from one alcoholic beverage to another. Unpleasant consequences with spouse, family members and associates no longer prevent drinking. Frequently unexplained changes develop in these relationships. Complaints about spouse, family and associates emerge. Medical excuses from work become frequent. Activities which are not directly associated with drinking are no longer of interest.

Tolerance allows the early alcoholic to function at alcohol levels that would incapacitate nondrinkers. It represents a relative resistance at a neuronal level to the effects of a given amount of alcohol. The alcohol-tolerant persons begins to show less effect per amount of alcohol consumed. He becomes "able to hold his liquor." He finds that "one or two drinks no longer work." Cross tolerance to other drugs develops, and less effects are noted from sleeping tablets and tranquilizers.[42]

Physical dependence, most notable in the classic alcohol withdrawal syndrome, is also operational in the early course of the disease during periods of abstinence. Withdrawal symptoms are initially intermittent, mild and cause little disability. However, in the background are 200 to 300 grams of daily alcohol consumption for many years, and considerable tolerance must have developed.[38] The spectrum of withdrawal symptoms is vast and several deserve mention. Tremor may initially be recognized as unsteadiness in drinking morning coffee or finding it necessary to change to an electric razor. Nausea, especially prevalent in the early morning after the most prolonged period of abstinence, is also frequent. It is commonly associated with vomiting, a reason many sufferers avoid breakfast. Sweating, occurring at night, is often noted as "nighttime clamminess" or "drenching soaks" which necessitate changing the bed clothes. Feelings of anxiety, impending doom or agitation may be noted. Early morning drinking quickly relieves these symptoms, at first.

Questions of intake deserve more comment. As previously noted, both timing and quantity are significant. However, as critical as the question itself is the manner in which it is answered. Weinburg has written that recognition of a patient's use of denial in answering may be of more diagnostic importance than a positive answer.[39] Early on, denial is used by the patient to avoid the reality of the issue, when a degree of dependence has already been established. Consequently, answers to consumption questions that are qualified in any manner become important. For instance, responses like "I drink, but only

beer" or "I drink, but never pass out," should be early clues to the presence of a potential problem. Denial is also reflected in attitudes reviewed earlier, but deserves reemphasis. Comments like "alcoholism is not a problem" or "drinking doesn't do anyone harm" should also make the interviewer alert to the possible presence of alcoholism. It is from the historical data base that important clues toward the earlier diagnosis of alcoholism can be developed. This history is difficult to pursue, requires in-depth understanding, patience and time, and mandates that the interviewer's attitude encourage communication about alcohol.[43,44]

This discussion has purposefully avoided the importance of physical examination or laboratory data. As a rule, there are only few early indicators of alcoholism in these data.[37,38] Tremor, mentioned previously, is occasionally present, appears after longest periods of abstinence and often requires close observation to document. Flushed facies is also an early sign. Two important findings, infrequently referred to, are tachycardia and hypertension, otherwise unexplained. These features assume more importance if they disappear after long periods of abstinence.

The odor of alcohol on a person's breath at the time of medical appointment is very indicative and a blood alcohol level of 100 mg per dl at that time is diagnostic of alcoholism.[37] Laboratory data which primarily reflect the pathophysiologic interference of normal metabolic pathways by alcohol provide some clues.[45-49] Therefore, hypoglycemia, hypophosphatemia, hypochloremic alkalosis, lactic acidosis, hyperuricemia, hypokalemia and hypertriglyceridemia may be present. Some investigators have supported macrocytosis alone as a very suggestive indicator of early alcoholism. Others have discussed the role of gammaglutamyl transpeptidase as an early sensitive finding.[50,51] At this time, these and other abnormal physical and laboratory information support the diagnosis. By themselves they do not establish the diagnosis. Neither does their absence rule it out.

Conclusion

If the availability of alcohol cannot be contained, the problem of alcoholism will likely remain in our society. To lessen its socioeconomic shock, prevention or earlier successful treatment must be realized. The latter goal demands earlier diagnosis, but either goal requires identification of persons at risk and recognition of early danger signals. Since the population of alcoholics is generated from a larger mass of problem drinkers and heavy alcohol consumers, information which describes these groups becomes diagnostically helpful; specifically from their demographic, cultural, social and familial characteristics and attitudes. In addition, if early historical clues are uncovered which result from dependence on alcohol, these may provide appropriate diagnostic information. Then to focus on risk factors and historical markers in alcoholism is important; though their presence does not establish the diagnosis, they should alert a physician that significant disease may be imminent. If the expectations of the medical profession include an earlier diagnosis of alcoholism, these historical danger signals must be uncovered. To await notable physical or laboratory abnormalities is to allow the disorder too strong a hold—one that may be irreversible.

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Exercise as Respiratory Therapy

THERE WAS A TREND (I hope it has been reversed) to tell patients with chronic respiratory disease to take it easy. . . . Respiratory cripples give up too soon, become inactive, become depressed, lose their self-image; and a tremendous vicious cycle is begun. They do this sometimes in the mistaken belief that if they simply do not strain their lungs and their hearts they will live longer. Then they really deteriorate and participate in their own downhill slide.

There is no question that you can train people with respiratory insufficiency to exercise more and be more comfortable. The mere act of exercise is not that important; what is important is translating this improved capability into activities of daily living. How that is translated into the patient's own life-style varies tremendously. But I have patients today who have continued to exercise and walk miles a day, after being housebound, because they love it. On the other hand, I have patients for whom exercise does not have much meaning. It is possible to train people; they can become more efficient physically and if this is useful for patients, then it is highly worthwhile.

—THOMAS L. PETTY, MD, *Denver*

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Cellular Basis of Anoxic-Ischemic Brain Injury

LT COL MICHAEL M. BRONSHVAG, MC, USA, *San Francisco*

Anoxic-ischemic cerebral disease is an important primary cause of morbidity and mortality, and also complicates a number of systemic diseases. Its clinical manifestations, such as hemiparesis and coma, represent cellular injury sustained by the complex, inhomogeneous brain. An understanding of the nature and pattern of anoxic-ischemic cerebral injury, and of the logical basis for avenues of therapy, is necessary to the management of patients with the various anoxic-ischemic disorders.

ANOXIC-ISCHEMIC BRAIN INJURY is an important primary cause of morbidity and death, and also frequently complicates systemic disease. Ischemia is defined as failure of tissue perfusion, and hypoxia is failure of tissue oxygenation despite adequate perfusion. Localized ischemic injury (stroke) is caused by cerebrovascular or cardiovascular disease. Generalized cerebral ischemia complicates a wide variety of clinical situations, including blood loss, sepsis and trauma. Hypoxia is most classically encountered in pulmonary disease, but hypoxic or hypoxic-like cerebral dysfunction complicates a wide variety of toxic-metabolic conditions. It is obvious that hypoxia and ischemia may occur simultaneously. Since hypoxia and ischemia produce roughly similar types of cellular dysfunction, the term "anoxic-ischemic brain injury" has clinical and experimental usefulness.

The brain is a complex, inhomogeneous organ composed chiefly of neurons, glia and vessels. The axons arising from neurons are coated by myelin-containing oligodendroglia so that most neurons with well-formed axons therefore exist in both gray matter and white matter.

The adult human brain stores little fuel,[1] has a high metabolic rate and has a continuing need for oxygen and glucose. Deprivation of oxygen or nutritive supply to the brain will result in death of the neurons,[2-4] with variable damage to glia and vessels.[5] Less clearly defined but of importance as a source of cerebral damage in ischemic states is the accumulation of toxic end-products and excess hydrogen. By contrast, the delivery of amino acids, fatty acids,[6] other substrates and vitamins is of lesser importance to the stated problem. Within the damaged areas, cellular elements will survive on the basis of adequacy of regional blood flow,[7] and of the basic ability of each cell type to withstand anoxic-ischemic insult.[4,8,9]

The neuron is the most sensitive brain cell and there is variability in the sensitivity of neurons in various layers and areas of the brain[2,10] (vide infra). Oligodendroglia, which synthesize and maintain myelin as an intracellular structure, are somewhat more resistant in acute anoxic-ischemic lesions; they may be preferentially damaged in certain situations involving a more sustained partial anoxic-ischemic insult.[11,12] Therefore, some patients may wake up from a hypoxic[13] or carbon

From the Clinical Investigation Service, Letterman Army Medical Center, Presidio of San Francisco.

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Reprint requests to: Lt Col Michael M. Bronshvag, MC, Box 365, Letterman Army Medical Center, Presidio of San Francisco, California 94129.

monoxemic[14] insult only to worsen days later due to massive subcortical demyelination caused by death of oligodendroglia. Astroglia, by contrast, are less affected by anoxic-ischemic injury.[5] They have relatively low concentrations of oxidative enzymes,[15] and well developed mechanisms for anaerobic glycolysis[16] and glycogen metabolism. However, they do have some potential for injury and swelling.[17] Blood vessels also tend to withstand anoxic-ischemic insult with less resultant damage,[5,18,19] unless there is direct vessel injury or blood stagnation (vide infra).

Therefore, although the various metabolic, cardiopulmonary and cerebrovascular diseases are studied per se, great interest has also centered about the responses of the neuron to insult. The neuron obviously tolerates the lesion in question for a period of time, then ceases to function and ultimately dies. We hope to understand the nonfunctioning, viable neuron when we face a suddenly comatose or hemiparetic patient; understanding exactly why it is dying may help us to tide it over the insult. Inherent in this obviously optimistic viewpoint is the concept of a weak link, a part of the neuron or its surroundings most susceptible to injury. This weak link may be an organelle, a membrane or an enzyme system. As discussed below, membrane, synapse, mitochondrion and enzyme systems have all been suspected of being the weak link, and the problem is unsolved. There may not be a weak link, or it may be different in each unique cause of anoxic-ischemic disease. Further, although we assume that bodily defense mechanisms are always wise, certain ones (such as hyperventilation and mitochondrial metabolism) are possibly deleterious, and a "defense" mechanism may be the weak link. Therefore, understanding selective vulnerability, patterns of cerebral response to injury (defense mechanisms) and weak links may guide therapy toward the goals of increased survival and minimized deficits.

Vascular Factors

The cerebral parenchyma has a high, continuous need for vascular support. Total cerebral blood flow varies relatively little between sleep and the various waking states,[20] as compared with skeletal muscle, whose blood flow may increase twentyfold during exercise,[21] and whose capillaries are perfused intermittently at rest. In fact, brain, heart and retina appear to be the only tissues whose capillary beds require continuous perfusion with arterial blood. More recent studies have shown there to be slight but definite increases in regional flow in cortex rendered active either by voluntary[22] (mental effort) or ictal[23] (focal seizures) factors. It has been deduced that blood flow is linked to cerebral activity; experiments employing direct measurements of regional cerebral metabolism using radioactive oxygen[24] or deoxyglucose[25] have confirmed this. The local messenger that generates regional vascular dilatation and increased regional flow is the hydrogen ion. In health the source of hydrogen ions is carbon dioxide ions (carbonic acid) generated by aerobic glycolysis. Therefore, the healthy neuron calls for more blood flow to remove byproducts of past efforts, and to supply fuel for further work. Locally generated hydrogen ions apparently diffuse into the extracellular fluid and thereby act directly on adjacent afferent arterioles. Local neurogenic regulation may also occur, and is the subject of renewed interest.[26,27] Some margin of safety exists, because modest decreases in cerebral blood flow, caused by, for example, hyperventilation or cardiovascular dysfunction, can be tolerated.

However, in more severe anoxic-ischemic lesions, whether focal or total, anaerobic glycolysis ensues and lactic acid accumulates. Unless the primary lesion was occlusive or vasospastic, the lactic acid causes vasodilation, and increased perfusion ensues. In severe lesions, hyperemia may persist into the postinsult period, causing persistent and perhaps unnecessary increases in regional cerebral blood flow (luxury perfusion).[28] The mediator of this postinsult vasodilation in damaged tissue may not be hydrogen, as it does not respond to hyperventilation.

Biochemical Changes

In the above anoxic-ischemic states, biochemical studies have shown there to be a switch to anaerobic glycolysis, and, in ischemia, depletion of glucose stores.[29] Lactate is generated, and the lactate-pyruvate ratio increases.[30] Energy rich adenylates dwindle as glycolysis fails to replenish the high energy phosphate bonds the neuron continuously requires; the ratio[31] of energy-rich to energy-poor adenylates fails.[32] At some point neurons fail to transmit impulses.[33] The changes occurring in the nonfunctioning but viable cell are of great theoretical and practical importance.

Cell death probably is caused by energy failure.[34] Most of the high energy phosphate bonds

are generated by mitochondrial metabolism, and the effect of hypoxia upon mitochondria is discussed below. The membranes and synaptic areas, deprived of energy sources, fail to transmit impulses. Further insult renders the membrane less able to maintain ionic gradients, presumably due to diminished activity of sodium-potassium adenosine triphosphatase and diminished levels of cyclic adenosine monophosphate. The synaptic areas undergo potential changes, loss of stored neurotransmitter material and ultimately loss of synaptic architecture. The point at which energy failure causes cell death is not known. Further, it is possible that the damaged neuron or axon may recover yet have irreversible synaptic damage.

The various anoxic-ischemic diseases have important biochemical differences. Hypoxia (anoxia) caused by exposure to oxygen-free atmospheres causes hyperventilation, pulmonary oxygen loss and alkalosis, while airway obstruction, as caused by aspiration of foreign bodies or (experimental) tracheal clamping causes respiratory acidosis. By contrast, in ischemic infarction end-products of anaerobic glycolysis and other cellular reactions cause local metabolic acidosis and local lactic acid accumulation,[7] while in hypoglycemia[11,18] (substrate deprivation) anaerobiasis cannot occur, and lactic acid does not accumulate. Hypotension due to blood loss of subacute onset resembles hypoxia in the diffuseness of the lesion;[19,35] there is a compensatory hyperventilation, arterial respiratory alkalosis, venous metabolic acidosis and elevation in circulating lactate.[36] By contrast, hypotension of sudden onset will, in addition to diffuse changes, cause areas of cerebral ischemia[19,35] and infarction in the border zones between major arterial territories, with attendant local metabolic and lactic acidosis. Strangulation[37] produces a complex picture of hypoxia, cerebral ischemia and venous stasis due to variable effects upon trachea, carotids and neck veins. Therefore, therapy to protect the neuron will augment, rather than replace, understanding and treatment of the specific disease causing anoxic-ischemic insult.

Electrophysiologic Changes

Microelectrodes placed in proximity to single neurons can record individual action potentials, which are of 1 to 2 millisecond duration (500 to 1,000 cycles per second or hertz[Hz]). The scalp recorded electroencephalogram (EEG) in the process of summing cortical activity, cannot detect these brief events, but instead records slower changes in synchronized postsynaptic cortical dendritic pools (2 to 20 Hz). These postsynaptic dendritic pool potentials are determined by the interaction of (1) ascending (precortical or presynaptic) activity generated by brainstem and thalamic centers and (2) cortical (postsynaptic) modulation. As a rule of thumb, the slower rhythms (2 to 7 Hz) indicate minimal or suboptimal cortical modulation of the slower ascending rhythms, and are seen in sleep, childhood and cerebral disease.

During advancing anoxia, the typical scalp recorded EEG shows the appearance of progressively slower and larger waves,[38-40] which may either be focal or generalized. These slow waves are presumably projected rhythms from deeper precortical structures,[41] unmodulated by the diseased cortex.[42] If the damage involves the entire brain, and "precortical" generation also fails, the slowing may be accompanied by voltage (amplitude) decreases, and, in severe cases, by electrocerebral silence, as shown by a "flat" EEG on scalp and cortical electrodes.

Parallel experimental study of individual cortical neurons shows that the earliest change is dendritic hyperpolarization (inhibitory postsynaptic potential (IPSP), followed by presynaptic depolarization. At this point the ("ascending" or "precortical") thalamocortical neurons can convey evoked action potentials, but synaptic failure occurs, due to the IPSP. More prolonged or severe lesions then cause afferent axonal terminals to discharge (leak ?) all of their releasable neurotransmitters; they are subsequently unstimulable.[43] This corresponds to the stage of electrocerebral silence and is correlated with loss of synaptic architecture.[44,45] Since postsynaptic unstimulability precedes presynaptic changes in lesions of gradual onset, the cortical neurons will tend to be unstimulable when bulk release of thalamocortical neurotransmitters occurs. However, in lesions of rapid onset, precortical neurotransmitter release may occur before postsynaptic unresponsiveness ensues, and paroxysmal cortical responses may be seen.[46] This presumably accounts for the occurrence of seizures in embolic events, cardiac standstill and hypoglycemia of sudden onset. Recovery from anoxic-ischemic insult is associated with return of more normal rhythms, occasionally associated with "spindling." Spindling[47] (runs of 15 to 30 Hz waves similar to spindles seen in arousal from normal sleep) apparently indicates

recovered thalamocortical intactness matched by recovered cortical modulating ability. A continuing "flat" EEG[48] suggests grave, irreversible brain damage[49] (if coexisting metabolic problems such as hypothermia, myxedema and sedative overdosage can be excluded), while recovery of EEG rhythm to normal frequency is usually associated with restoration of consciousness and some restoration of neurologic function. However, alpha coma[50] (an apparently "normal" basic alpha rhythm of 8 to 11 Hz, prominent frontally, and unresponsive to stimuli in a comatose patient) may occur after diffuse anoxic-ischemic insult, and has a poor prognosis. By contrast, the normal alpha rhythm is most prominent occipitally and suppresses in response to noise or similar stimuli, and in response to mental effort.

The sequential occurrence of cortical hyperpolarization and thalamocortical depolarization may be marked by measurable changes in extracellular fluid content. The neuronal IPSP is presumably generated by increased intracellular chloride and may be associated with slight local increases in potassium. The presynaptic depolarization releases measurable amounts of potassium[51] and neurotransmitters[52,53] into the extracellular fluid and cerebrospinal fluid. The appearance of altered levels of potassium or neurotransmitters in the parenchyma[54] or cerebrospinal fluid[55] unaccompanied by gross leakage of cytoplasmic or membrane components (lipids, enzymes) may mark the distressed, nonfunctioning viable cell. The released neurotransmitters may[53] or may not[56] cause increased ischemia through increase in local vasospasm.

Histologic Changes

Light and electronmicroscopic study of anoxic-ischemic neurons suggests that the first identifiable microscopic change is cytoplasmic microvesiculation, which is due to swelling of mitochondria.[2,57] Whether this change represents mitochondrial damage or is a response to damage elsewhere in the cell will be discussed below. More severe or prolonged anoxic-ischemic injury causes the appearance of the Spielmeyer ischemic neuron.[58] This dead neuron has a pyknotic nucleus with absent nucleolus, and homogeneous, eosinophilic cytoplasm, corresponding to loss of nuclear (nucleolar) and cytoplasmic ribonucleoprotein. It classically appears several hours to several days after a significant anoxic-ischemic insult and suggests that the highly energy-dependent step of ribonucleic acid (RNA)-mediated protein synthesis has been interrupted. Often ischemic cell change is accompanied by cytoplasmic incrustations,[57] which are condensations of dead cytoplasm. Because infarcted cardiac muscle mitochondria may mineralize,[59] and because diseased skeletal muscle mitochondria may accumulate hydroxyapatite,[60] it is possible that the focus for the cerebral incrustations described is also the mitochondrion.

It must be noted that the commonest change seen microscopically is not the Spielmeyer change but simply cell dissolution and disappearance. Various other combinations of nonartifactual nuclear and cytoplasmic swelling or shrinkage have also been described[61] in response to injury.

Ischemic damage to subcortical white matter may similarly cause the death of axons or oligodendroglia. Damage to the synaptic apparatus may cause failure of cerebral function with essentially no cell death[62] and therefore essentially normal histology. This type of lesion may account for those patients who have severe neurologic deficits after anoxic-ischemic insults but whose brains at necropsy are described as normal after standard examination. Methods capable of studying synaptic histology and ultrahistology[62,63] may prove valuable in such cases. Endothelial cells are relatively resistant to anoxic-ischemic injury, but they may be damaged in massive lesions. They have also been observed to swell in response to anoxic-ischemic injury and may cause secondary obliteration of the capillary lumens in the hours after injury, with attendant ischemia (the no-reflow phenomenon[64-66]). The cause of the no-reflow phenomenon in various anoxic-ischemic states has been debated at length, but it seems most reasonable to incriminate vascular stagnation as the most common cause of endothelial injury yielding no-reflow. Other factors, such as simple endothelial cell anoxia may play a role. It is debated whether no-reflow is a clinical cause of secondary ischemia or merely marks severely damaged areas. Since no-reflow may be prevented (experimentally) by continued perfusion with normal saline and treated (again experimentally) with diuretics, this question is of great clinical importance.[62]

Cerebral Edema

Anoxic-ischemic cerebral injury may be complicated by cerebral edema. Cerebral edema is simply defined as an increase in tissue content of water or fluid. This fluid may be either of low

protein content (crystalloid) and primarily intracellular, or of high protein content (colloid) and primarily extracellular. The former edema (termed cytotoxic)[68] represents imbibition of water by cells with dysfunctional membranes. The latter (termed vasogenic)[68] represents leakage of serum protein between cerebral capillary endothelial cells.[69,70] Unlike systemic endothelial cells, cerebral capillary endothelial cells are bound to each other by tight junctions (occluding zonules) and are, in health, impermeable to colloid-sized molecules (blood-brain barrier to albumin-sized molecules); therefore this latter vasogenic edema is synonymous with breakdown of the blood-brain barrier.

If a sizable number of neurons die, ischemic cerebral edema appears within several hours. This edema is mainly due to increases in water and crystalloid in the damaged and dying cells[71-73] and in the extracellular fluid,[74] and presumably reflects decreased or lost ability of neuronal membranes to maintain ionic gradients. It is a cytotoxic[72] edema, and does not imply a blood-brain barrier defect (vasogenic edema).

Because acute ischemic brain damage affects glia and vessels less than neurons, acute ischemic infarction will usually not cause immediate permeability to albumin-sized particles, despite the rapid appearance of ischemic edema. However, as the cellular response to brain infarction evolves, new capillaries grow into the area to enable the phagocytic microglia and blood-derived macrophages to carry debris away.[75] These new vessels resemble systemic vessels in that they do not have tight junctions, and they leak albumin[76] into the extracellular space of the brain, predominantly the subcortical white matter. Since the brain does not have a lymphatic system for removal of extracellular protein, this high-protein (vasogenic) edema accumulates in the extracellular compartment. It eventually migrates toward the ventricular surface and into the cerebrospinal fluid, and may measurably elevate the cerebrospinal fluid protein level.

Ischemic cerebral edema may cause significant increases in the volume of an infarcted area in the first days after the insult. Since the brain is confined by the rigid skull, compensation is attempted by decrease in volume of the cerebrospinal fluid and vascular compartments in adjacent normal brain. The further response to uncompensated acute ischemic cerebral edema is herniation, with additional central nervous system damage or death.

By contrast vasogenic cerebral edema is caused by neovascularization and is more indolent in its accumulation, becoming maximal in the second week after injury. It is a cause of secondary cerebral dysfunction in cases of cerebral tumor, but appears to be well tolerated in anoxic-ischemic diseases.

Ischemic cerebral edema differs from edema secondary to water intoxication in that the primary disturbance in the former state is to the cell membrane. Since osmotic agents, effective in water intoxication, require functioning membranes in order to exert their dehydrating effect, they will have minimal effect in infarcted tissue. Apparently their major therapeutic effect in ischemic edema is to shrink adjacent normal brain tissue and allow the infarcted tissues to expand without causing herniation.

Anoxic-ischemic disease that kills scattered neurons but does not produce any zones of necrosis (infarctions) may cause a devastating clinical deficit, but will not arouse the above-described cellular response. Edema formation may be minimal or diffuse.

Certain experimental and clinical causes of ischemic brain death also damage the endothelial cells per primum;[77] examples of this are air[78] or oil[79] emboli, fragmenting clot emboli,[77,80] local trauma,[81,82] rapid reestablishment of flow to an infarcted and edematous area (by clot dissolution, hypertension-induced increase in collateral perfusion or ill-timed vascular surgery) and venous thrombosis.[83] Indeed, in some experimental models of embolic disease, acute transient breakdown of the blood-brain barrier to albumin without neuronal injury has been shown. However, chronic vasogenic leaks will injure healthy cerebral tissue.[84]

Brain Scans

The nuclide brain scan is done by administering a radionuclide which either complexes with albumin or behaves like albumin, and therefore recirculates. Because most capillary beds are permeable to albumin, and because the nuclide will be specifically taken up by certain tissues (thyroid, stomach, reticuloendothelial system, choroid plexus for example), tissue concentrations of radionuclide will gradually increase as circulating levels are dropping. However, brain tissue con-

centrations of nuclide will not increase unless there is an increase in tissue permeability to albumin (breakdown in the blood-brain barrier). Therefore, in brain views taken immediately after administration of nuclide (dynamic, flow or perfusion views) localized decrease in nuclide emission may indicate failure of perfusion, as seen in occlusion of a large vessel (usually an internal carotid), and a localized increase in emission may indicate reactive hyperemia with increase in local intravascular volume and flow (luxury perfusion). Delayed views (static views), if positive, indicate a breakdown in the blood-brain barrier to albumin. Therefore, static views obtained immediately after the onset of ischemic infarction will usually be negative and repeat static views obtained one to two weeks later are often positive, indicating neovascularization (see above).[76,85] In infarctions complicated by significant primary endothelial damage[77]—such as hemorrhagic infarction of any cause, and those caused by air[78] or oil[79] emboli, many thromboemboli,[77,80] local trauma[81,82] or venous thrombosis[83]—there will be immediate permeability of the brain vessels to albumin; the static nuclide brain scan will be immediately positive as a reflection of vascular rather than parenchymal changes. As mentioned above, in some experimental models of embolic disease, acute transient breakdown of the blood-brain barrier to albumin has been caused by osmotic shrinking of endothelial cells,[84] unaccompanied by parenchymal damage. In those models nuclide brain scanning could be positive in the absence of damage to brain parenchyma.

The computer-assisted tomographic scan (CT scan) is able to distinguish density differences between water (cerebrospinal fluid) and brain tissue and can thereby depict brain anatomy much as a plain chest film depicts heart-lung-bone anatomy. CT studies of patients with acute ischemic cerebral infarction have shown the early appearance of low (water) density areas in the affected parenchyma; this undoubtedly represents ischemic cerebral edema.[19] Intravenous injection of iodinated dyes (contrast or opaque) causes an increase in the density of blood, which the CT scanner is able to detect. Thus, analogous to the situation with the nuclide scanner, if the contrast-enhanced CT scan shows early localized increase in density, hyperemia may be present, while localized increases in tissue density seen on delayed scans (excessive contrast enhancement) represent breakdown of the blood-brain barrier to large molecules.[86]

Anoxic-ischemic disease that kills scattered neurons but does not produce any zones of necrosis (infarctions) may cause pronounced neurological deficits or even death, but edema formation, vascular change and cellular reaction may be minimal or diffuse, and the CT and nuclide brain scans may give negative findings.

Selective Vulnerability

As mentioned above, the brain is inhomogeneous with regard to structure, blood supply and function. Generalized lesions such as hypoxia and diffuse ischemia do not affect all parts of the brain uniformly. The resulting selective lesions discussed below may cause distinctive patterns of neurologic dysfunction,[10] and enable physicians to make clinical-pathological correlations. Of greater importance to therapy-seeking clinicians or researchers is the tempting clue these selective lesions proffer; if one part of the brain is weaker, then another must be stronger. If so, why, and how can we convert this knowledge into therapy?

Anoxic lesions relatively selectively damage layers 3 and 5 of the cerebral cortex, the Sommer sector of the hippocampus and the Purkinje neuron layer of the cerebellum. The basal ganglia are variably affected, and the brainstem and spinal cord tend to escape damage. In newborns, the brainstem nuclei may be especially sensitive, and suffer more severe injury than the cerebral cortex.[87-90] For several decades, the theories advanced to explain this phenomenon are the susceptible cell theory (Vogt), which postulates that under equal conditions of anoxia, metabolically more vulnerable cells will suffer damage first, and the vascular theory (Spielmeyer[58]), which postulates that an anoxic stress is rendered nonuniform by local variations in vascular adequacy. The two theories are not exclusive of each other. In hemorrhagic shock of gradual onset, ischemic neurons are found throughout the cortex in a typical anoxic distribution (sparing the hippocampus), but, if the blood pressure is dropped precipitously, ischemic neurons and small areas of pan-necrosis (infarcts) are found in the border zones between the arterial territories.[19,35] This suggests that both the cell and vascular theories apply. In the Levine preparation[13] (ligation of one carotid artery plus exposure of the animal to an oxygen-free environment until unconsciousness

supervenes), the anoxic changes are found only in the hemisphere ipsilateral to the ligature; that is, the lesion is generated by anoxia plus ischemia. More recent study[3] of the model has shown that the infarcted hemisphere had no decline in tissue concentrations of glucose substrate despite severe lactic acidosis, changes compatible with anoxia rather than ischemia. Cerebral blood flow in the affected hemisphere actually increased 20 percent and contralateral cerebral blood flow increased 80 percent. Apparently a 20 percent increase in blood flow did not compensate for hypoxia, but 80 percent did. The authors therefore concluded that a vascular lesion led to a hypoxic injury, truly a combined lesion. Therefore, selective vulnerability appears to be determined by the nature of the lesion and properties of the brain.

To reiterate, blood flow is not equal in all parts of the brain,[91] and all areas of the brain have a safety factor, a degree of ischemia that can be tolerated.[10] Although total cerebral blood flow and nutritive delivery may average out to be adequate for the entire brain, ischemia may exist in, for example, layer 5 of the cerebral cortex or in the Sommer sector of the hippocampus; an apparently uniform lesion may therefore be modified by vascular factors.

Moreover, the effect of an anoxic-ischemic lesion may be greatly modified by associated metabolic events. As reviewed by Siesjö,[92] the tolerance of rats to anoxia was studied. Tracheal occlusion was tolerated for longer periods than exposure to 100 percent nitrogen, with parallel increases in time that the rats could sustain cerebral perfusion. Apparently nitrogen breathing caused hyperventilation and significant pulmonary oxygen loss, while asphyxia caused carbon dioxide retention with attendant cerebral vasodilation. In a clinical study,[92,93] mental performance during moderate hypoxia improved if carbon dioxide was administered. The carbon dioxide prevented loss of consciousness and electroencephalographic[94] changes. Since the response of the intact subject to hypoxia is hyperventilation, with respiratory alkalosis and cerebral vasoconstriction, the carbon dioxide was presumably increasing cerebral blood flow and therefore increasing oxygen uptake by cerebral parenchyma.

The concept of local vascular adequacy is also pertinent to the evaluation of hypoglycemia.[11] Hypoglycemia, like anoxia, is a systemic disease with prominent cerebral dysfunction. Hypoglycemia resembles anoxia pathologically, and like anoxia can be modified by vascular factors. The brain arteriovenous glucose difference in health is about 10 mg per dl, and, therefore, a mixed venous glucose level of 10 mg per dl and an arterial glucose value of 20 percent should theoretically not cause hypoglycemic brain injury. Since it obviously does, one can speculate that certain brain areas have venous glucose levels of zero, indicating locally inadequate safety margins.

Further, secondary circulatory derangements, due to compressed or constricted vessel lumens, if present, may increase the severity of a lesion. Ischemic diseases[7] may cause prominent and early vascular stagnation, while in asphyxia, circulatory failure may only be agonal.[7] Hemorrhagic hypotension of gradual onset does not cause infarction or stagnation,[18] while precipitous drops in blood pressure cause border zone infarction[18] and perhaps stagnation. Therefore, although the clinical spectrum of secondary vessel changes and no-reflow is uncertain, it may be of significance in occlusive infarction and exsanguination, and of little import in hypoxia.

Weak Link

The susceptible cell theory (of Vogt) is based on the observation that certain cell groups are damaged in anoxic lesions where there is little or no evident inhomogeneity of the insult. It suggests that by virtue of inherent metabolic differences, certain neurons are more or less susceptible to anoxic damage. Since anoxic-ischemic lesions do not affect all subcellular systems equally, it is possible that a specific subcellular structure, process or function is selectively damaged in anoxic-ischemic lesions. It is further possible that this weak link varies in its susceptibility in different populations of neurons, and that this weak link may be strengthened by appropriate prophylaxis or treatment. It is, of course, possible that the neuron, like the one-horse shay, falls apart at once; it is equally possible that the weak link is different in the various anoxic-ischemic diseases. Neither of these possibilities, if true, would make neuronal salvage impossible, but it is obviously easier to attempt modification of a single subcellular process than to beneficially alter all cell functions.

Because the mitochondrion regulates cellular energy metabolism, and because mitochondrial abnormalities are present in early anoxic-ischemic lesions, the mitochondrion was suspected of being

the weak link. However, most, but not all,[95] studies of mitochondrial ability to generate high energy phosphate bonds and to maintain appropriate coupling of metabolic rate to substrate availability have shown their resistance to hypoxic-ischemic insult, even at tissue oxygen pressure frankly incompatible with life.[96,97] Further, mitochondrial swelling has been shown to exist in a variety of situations in which mitochondrial function has remained intact.[98] Ultrastructural studies of rat liver mitochondria suspended in 2 percent potassium permanganate solution have shown cristal swelling accompanied by increased active transport of potassium when valinomycin was added. This swelling was interrupted by hypoxia. The authors regarded the swelling as an energy-requiring active process.[99] By contrast, addition of calcium chloride and inorganic phosphate caused irreversible swelling of the matrix space. Therefore, certain types of mitochondrial swelling may be a reactive process, and may merely serve to mark the altered or diseased cell. Our experiments producing hemorrhagic shock in unanesthetized sheep have shown swollen mitochondria in sheep bled incrementally into hemorrhagic shock. The sheep were awake when biopsy specimens were taken. (Bronshvag, M: Unpublished, current data.) These findings also suggest that the mitochondrion was not the weak link and the mitochondrial swelling might be a reaction rather than a lesion.

As much as half of the energy requirements of the neuron go to maintaining the membrane[92,96] (much of it through the sodium-potassium ATPase pump). Loss of membrane structural integrity has been shown in anoxic neurons whose mitochondrial function remained normal.[100] Compressive ischemia has caused release of synaptic membrane antigen[44] and altered synaptic ultrahistology[45] as early changes. Therefore, many investigators[45,100] now regard the membrane or synapse as the weak link. Others describe early changes in synthesis of lipids,[101] nucleic acids or protein.[102] Research biochemists, ultrahistologists or physiologists may be just one step away from helping clinicians treat hemiparesis or coma.

Reversibility

A neuron or brain exposed to an anoxic-ischemic insult will continue to function for a time, then cease functioning but continue to be viable, and subsequently succumb to the lesion. There are two crucial questions: How long can the neuron withstand an unmodified lesion? What effect will therapy have upon reversibility of the insult? It is a fairly well accepted rule of thumb that the human brain can withstand cardiac arrest or total local vascular occlusion for three to five minutes, and may withstand anoxia with maintained circulation for perhaps twice that time. However, the experiments designed to shed light on this problem have led to contradiction and confusion.[8] To begin with, although one would assume that complete anoxia or ischemia is more poorly tolerated than a partial lesion, there is evidence to the contrary.[9] If this conclusion were to be taken literally, its practical implications would be rather frightening. It seems that stagnation of blood (no-reflow[64,66]) and continued cardiorespiratory problems[58] (postanoxic hypotension[9,96]) may increase the severity of cerebral damage. This may explain why some patients with a short period of arrest may never awaken. Some investigators[9] have described preserved cerebral function in mammals, including primates, exposed to an hour of normothermic ischemia and 20 hours of local occlusion. These results, if meaningful for clinical situations, may have more relevance to focal problems (stroke) than to diffuse problems; they, in any event, encourage clinicians and researchers not to give up hope. On the other hand, some patients may apparently recover from an anoxic-ischemic insult, only to later worsen or die, due to delayed demyelination.[13,14] It appears that oligodendroglia sustain damage to some subcellular organelle not required for minute-to-minute survival of the cell, but required for its continued structural integrity. Although similar phenomena requiring neuronal cell bodies have not been described clinically, experimental evidence exists that submassive anoxic-ischemic lesions may cause delayed neuronal dysfunction and death.[103] These lesions require one to two weeks to "mature," and the neurons are apparently functioning during this time. We do not know whether these "maturing, delayed" lesions are of great clinical import; if so, they would be maturing while the comatose or plegic patients are under medical supervision, and well might be amenable to appropriate therapy.

Therapy

At present, clinicians are largely limited to supportive care and to recognition of unsuspected concurrent conditions (hypoglycemia, multiple pulmonary emboli, bacterial meningitis and the

like). Specific therapy to correct oxygen deficits (hyperbaric oxygen)[104] or related cellular metabolic demands (hypothermia)[105] is of proven value experimentally, but is poorly adapted to roadway, emergency ward and battlefield realities. Since therapy which retards cellular metabolism is of benefit experimentally, the role of barbiturates is being studied clinically[106] and experimentally[107] in the various anoxic-ischemic diseases, to better define the potential role of this type of agent. Barbiturates appear to retard metabolism by partially blocking electron transfer through the cytochrome chain,[96] but may have other subcellular effects.

As mentioned above, 5 percent carbon dioxide is a vasodilator, and is of some prophylactic benefit in one infrequently encountered clinical setting. Its major effect appears to be upon normal blood vessels; as blood vessels in anoxic-ischemic areas are already maximally vasodilated (luxury perfusion, reactive hyperemia), carbon dioxide may, therefore, shunt blood away from ischemic areas (reverse steal). Carbon dioxide also depresses cerebral activity and increases permeability of cerebral capillaries to albumin. It may, therefore, cause cytotoxic and vasogenic edema,[108] and may dangerously elevate intracranial pressure. It is valueless when localized or systemic acidosis is present,[92] and probably cannot increase vasodilation after termination of an insult.[109] This potentially toxic agent appears to have essentially no clinical role.

By contrast, hypocapnia induced by forced hyperventilation will cause vasoconstriction in normal brain tissue. It is of theoretical benefit in cases of focal ischemia (that is, stroke) because it should shunt blood from healthy areas to oxygen-poor ones, but seems not to be strikingly effective. Hyperventilation also reduces vascular volume by causing vasoconstriction. It is useful in neurosurgical anaesthesia,[110] can lower intracranial pressure and can reverse incipient brain herniation in patients with anoxic-ischemic cerebral lesions.

Corticosteroids are effective in reversing the vasogenic edema produced by altered blood vessels adjacent to tumors,[111] but are ineffective in reversing vasogenic edema caused by direct vessel injury such as cold-induced cortical lesions.[112] They probably only have slight effect upon the delayed, well-tolerated vasogenic postinfarction edema. Steroids also have little beneficial effect upon ischemic cerebral edema.[113] In sum, they may[73] or may not[113] be of some benefit in anoxic-ischemic disease. Many clinicians reserve their use for cases in which cerebral edema is causing further morbidity, and then use rather high doses of agents such as dexamethasone. Osmotic diuretics may be of some further benefit in such cases.[114,115] Xanthines,[116] which retard breakdown of cyclic AMP and may therefore diminish energy requirements of distressed cells, are also under investigation.

In summary, in evaluating the neuronal response to an anoxic-ischemic insult, one must evaluate several factors, as outlined below:

- *Flow factors.* Does the lesion interrupt blood flow? To what extent? Where, diffusely? In a vascular territory? In a border zone? Is there capillary stagnation?
- *Nutritive factors.* Does the lesion deprive oxygen? Glucose? Other factors? Is lactate produced? Does it accumulate?
- *General factors.* What is the patient's overall condition? Is he anaesthetized? Hypothermic? What is his status after injury? Hypotensive or hypertensive? Apneic?
- *Evaluating the lesion.* What is the nature and distribution of the lesion produced? Diffuse? Focal? Multifocal? Is the blood-brain barrier intact?
- *Electroencephalograph.* Does an electroencephalograph show slowing? Flattening? Spindling? Nonreactive alpha?
- *Changes.* Are there delayed changes? No reflow? Demyelination? Recurrence of the original problem?
- *Therapy.* Are there specific therapeutic implications? Oxygen? Glucose? Steroids? Osmotic agents? Other medical or neurosurgical modalities?

The above approach will enable a clinician to understand the pathophysiology in a patient or experimental animal with anoxic-ischemic brain injury, and to interpret research protocols employing drugs or treatments of potential benefit to his patient.

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A Predictive Study of Congenital Heart Disease and Need for Care

NIGEL ROBERTS, MD, *Los Angeles*

For long-term planning in the delivery of health care, prevalence data are essential for budget estimates in terms both of distribution and training of manpower and fiscal responsibility. From incidence figures, from the knowledge of the natural history of congenital heart disease and from predicted population estimates it is possible to construct a model that reflects the prevalence of congenital heart disease. This has been done for the state of California; the methods used and the data gathered should prove useful nationally.

It is estimated that there were in 1975 in California 17,531 children under 21 years of age with congenital heart disease; 24 percent of these had ventricular septal defects and 23 percent had pulmonary stenosis, 11 percent had atrial septal defects and 9 percent had aortic stenosis; the other forms of congenital heart disease constituted the remaining 33 percent. Based on these estimates it is then possible to plan the medical resources necessary for optimal care.

ESTIMATES of the incidence of congenital cardiac malformations* are now available.[1-3] It is difficult, however, to use these estimates for the determination of the prevalence of congenital cardiac malformations† because the incidence data fail to include attrition through death or recovery. For long-term planning in the delivery of health care, prevalence data are essential for budget estimates in terms both of distribution of manpower and fiscal responsibility.

A recent report[4] to the California legislature on the California Crippled Children Services concludes that for determinations of case finding effectiveness and for the establishment of objectives and priorities for future program operations it is necessary to find a meaningful point prevalence of the handicapped population. The report goes on to say that it would be possible to obtain detailed and useful figures on the population by conducting an extensive state survey based on a health examination survey. The report, however, concludes that such a survey probably would be exorbitantly expensive in terms of its benefits.

The purpose of this study is to use incidence and attrition data to create a model that reflects the expected prevalence of congenital cardiac malformations in California. Requirements for the delivery and maintenance of health care can then be assessed.

Specifically the objects of this study are the following: (1) to assess the number of cases of congenital cardiovascular malformation for a given year in the California population under 21 years of age. (2) To delineate the different types

*Incidence is the occurrence of congenital heart disease during a given period.

†Prevalence represents the proportion of the population with congenital heart disease at a particular time. The general relationship of prevalence (P) and incidence (I) may be expressed as $P = I \times D$, where D is duration of the disease in an individual case expressed with same time units as I.

From the Division of Cardiology, Department of Medicine and Pediatrics, University of California, Los Angeles, School of Medicine.

Submitted September 1, 1977.

Reprint requests to: Nigel Roberts, MD, Department of Pediatrics, UCLA School of Medicine, Los Angeles, CA 90024.

TABLE 1.—*Predicted Population of California*[7] *and Estimated Live Births* for Selected Years Between 1975 and 1994*

	Population	*Live Births*
1975	21,206,000	329,000
1980	22,659,000	351,000
1985	24,363,000	378,000
1990	26,098,000	405,000
1995	27,726,000	429,753

*A live birth rate of 15.5 is assumed.

TABLE 2.—*Incidence of Congenital Heart Disease Based on a Mean Three-Year Observation of 54,765 Children*[3]

54,765	Live births	
420	Children with congenital heart disease	7.7*
	78 Children died before 28 days	
	50 Children died between 28 days and 1 year	
	20 Children died after 1 year	
272	Children with congenital heart disease survived for an average of three years	5.3*

*Incidence of congenital heart disease per 1,000 live births

of congenital cardiac malformations assessed. (3) To show that such predictions may be used to assess the extent of required health care resources.

It is important to note that the population of California is almost a tenth of the total population of the United States. The United States Health Department's 1970 population figures for California and the nation were 20 million and 203 million people, respectively; the 1975 figures were 21 million and 213 million, respectively.

Materials and Methods

The population under consideration for this study is that of the state of California. From predictions of the number of live births in California from 1975 to 1994 it is possible by the use of incidence figures to estimate the number of children who would be born with congenital heart disease each year. Those children born in the final year and all the children from previous years who enter the second year of life are then added together over the 20-year period. The total estimate for the cases of congenital heart disease in 1994 is, however, much larger than the actual prevalence of congenital heart disease in the under 21-year-old children because this number fails to include either an estimated attrition through spontaneous improvement or death or to exclude those children who reach twenty years of age.

By the use of such a predictive study, which is the same length in years as the upper age limit of the studied cohort, one is able to ensure that at the end of the 20-year period, all the children included will be those who have been predicted and that all the children will be 20 years old or less.

A knowledge of the natural history and surgical management is then applied to the individual lesions. With respect to congenital heart disease the prevalence of heart disease in the 20-year-old and under group can therefore be regarded:

Prevalence of congenital heart disease in those under 21 years of age in California equals (yearly California population for 20 years × live birth rate : 1,000) × (incidence of congenital heart disease : 1,000) minus (the children expected to die in the first year of life in each of the first 19 years of the study + the spontaneous improvement rate + the premature death rate).

From California population predictions and live birth rates are determined the numbers of children expected to be born (Table 1). Incidence figures for congenital heart disease are then used to estimate the predicted number of cases (Table 2). For the years 1975 through 1994 all the children with congenital heart disease are added up.

From this total are subtracted all those born between 1975 and 1993 who fail to survive for one year, those who would be expected spontaneously to improve and those who would be expected prematurely to die. This figure would reflect the number of children up to the age of 20 with congenital heart disease in California in 1994. A prevalence ratio is then determined.

In order to avoid the necessity of carrying out an analysis for attrition through spontaneous improvement or death for each of the years between 1975 and 1994, a yearly estimate of survivors of children with congenital heart disease born in 1975 is then made (Table 3). Similarly, estimates are made for each individual cardiac lesion. These estimates are then proportionally increased by a population factor which represents the yearly increase in California population (Table 4). The total estimate of congenital heart disease can then be used to derive a prevalence ratio for 1994.

For children with ventricular septal defects and with pulmonary stenosis, the health care require-

TABLE 3.—*Yearly Estimate of Survivors of Children With Congenital Heart Disease Born in 1975*

Year	*Year of Life*	*Number of Children*	*Population Factor**
1975	<1	2,520	1.29
1976	2	1,460	1.27
1977	3	1,304	1.25
1978	4	1,147	1.24
1979	5	1,104	1.23
1980	6	1,061	1.21
1981	7	1,018	1.19
1982	8	975	1.17
1983	9	933	1.16
1984	10	891	1.15
1985	11	849	1.13
1986	12	820	1.11
1987	13	791	1.10
1988	14	762	1.08
1989	15	733	1.07
1990	16	704	1.06
1991	17	675	1.04
1992	18	646	1.02
1993	19	617	1.01
1994	20	589	1.00

*Population factor is the population of California in 1994 divided by the population in the index year. For instance in 1980, the population factor $= \frac{27,435,400}{22,659,000} = 1.21$

TABLE 4.—*Estimated Numbers of Children With Congenital Heart Disease in California in 1995*

Year of Birth	*Year of Life*	*Number of Children**
1994	1	3,251
1993	2	1,854
1992	3	1,630
1991	4	1,442
1990	5	1,358
1989	6	1,284
1988	7	1,211
1987	8	1,141
1986	9	1,082
1985	10	1,025
1984	11	959
1983	12	910
1982	13	870
1981	14	822
1980	15	784
1979	16	746
1978	17	702
1977	18	659
1976	19	623
1975	20	589
TOTAL		22,922

(Number of cases in 1995 × 100 ÷ California population in 1995)
Prevalence Ratio = 0.078

*This number represents the childen who survived until 1995 from those born in the year listed alongside the number. The number of children is obtained in each year of birth by proportionately increasing the number of children in a certain year of life in Table 3 by the population factor. For instance, in Table 3 in the fifth year of life there are estimated to be 1,104 survivors of children born in 1975. However, children alive in 1995 who were in their fifth year of life would have been born in 1990. Consequently 1,104 × 1.23 (from Table 3) equals 1,358 (Table 4)

ments are estimated and compared with those actually rendered in California.

Major assumptions in this study include a relatively stable live birth rate, a predicted population growth, stable incidence figures for heart disease and a similar death rate in serious cardiac lesions and a constant prevalence ratio. A live birth rate of 15.5 per 1,000 population is used because it is the most recently available figure (1974)[5] and it is more likely to represent future figures rather than the high figures of the early 1970's.[6] The estimates for predicted population were obtained from the California State Department of Finance in Sacramento. The D-100 series was favored over other state and federal estimates because it takes into account not only the fertility rate but the migration rate and local factors.[7] The incidence data for the frequency for congenital heart disease were obtained from the Perinatal Research Branch, National Institutes of Health, Bethesda, Maryland.[3] The incidence of congenital heart disease in this study was estimated after data were obtained after a mean follow-up period of three years. In a further long-term study by Dr. Julien Hoffman, Professor of Pediatrics at the University of California, San Francisco, by 36 months of age over 98 percent of congenital heart disease had been located. It is realized, however, that the incidence figures for congenital heart disease are primarily obtained from a low socioeconomic group,[3] but the incidence figures are very similar to those obtained by Dr. Hoffman from the San Francisco Bay area of California. This latter group reflects all the major racial and socioeconomic groups with the exception of the very affluent.

The final assumptions were that the natural history studies of children with ventricular septal defects[8,9] reflected the distribution of small, moderate and large defects and that corrective cardiac surgical treatment results would not worsen.

It is to be emphasized that this study concerns itself with congenital heart disease and does not include rheumatic, atherosclerotic and hypertensive heart disease. Since accurate data are unavailable for the incidence of patent ductus arteriosus in premature children, bicuspid aortic valves and for prolapsed mitral valves, these three conditions have been omitted.

Results

Live births in California estimated from a live birth rate of 15.5 per thousand and from the predicted population are tabulated alongside repre-

sentative years (1975, 1980, 1985, 1990 and 1995 [Table 1]).

After the estimation of the live births per year is made, the incidence of specific cases of congenital heart disease is predicted. An example year is tabulated as Table 5. The lesions are listed under five columns. The first column is the total number of defects at birth, the next three columns represent, respectively, children who had cardiac lesions and died within 28 days of birth, between 28 days and one year, and after one year. The remaining column represents those children who would be expected to live longer than one year. Addition of these estimates indicates that there would be 40,038 children with congenital heart disease under 20 years of age in 1995.

This estimate, however, fails to include attrition through spontaneous improvement or death. Recovery of children with congenital heart disease is due predominantly to spontaneous closure of defects of the ventricular septum and closure of the ductus arteriosus. Mortality statistics for sudden death and from specific cardiac surgical procedures are also used.

As an example, Table 6 represents attrition in children born in 1975 with ventricular septal defects. By 1994 (when children born in 1975 are in their 20th year) it is expected that there would be at most 168 with ventricular septal defects. Each of the major groupings of cardiac conditions went through a similar analysis. It was estimated that each year there would be 411 children under the age of ten years who would undergo open heart surgery in California. This figure would include 80 children with pulmonary stenosis, 100 children with atrial septal defects, 60 children with coarctation of the aorta, 30 children with aortic stenosis, 66 children with the tetralogy of Fallot and 75 with miscellaneous conditions. It was estimated that 8 percent of these procedures would result in death. These figures are comparable to the figures prepared by the

TABLE 6.—*Estimated Attrition of Children Born in 1975 With Ventricular Septal Defects (VSD)*

1975	810 children born with VSD[3] ..	=810
1976	810 minus 84 children who die in first year[3] and 292 VSD that spontaneously close[8]	=434
1977	434 minus 170 VSD that close spontaneously which represent 75 percent of the remaining 227 small VSD's[6]	=264
1978-1984	264 minus 57 VSD's that close spontaneously which represents 25 percent of the remaining 227 small VSD's and 12 which represent deaths from attempted surgical closure	1984 = 177
1985-1994	177 minus 9 which represent deaths from attempted surgical closure	1994 = 168

TABLE 5.—*California Children Born With Congenital Heart Disease in 1975. Expected on Basis of Data Collected by Mitchell et al. 1973*[3]

	At Birth	*Died <28 Days*	*Died 28 Days to 1 Year*	*Died >1 Year*	*Survived for a Mean of Three Years*
Ventricular septal defect	810	54	30	18	708
Pulmonary stenosis	282	30	..	6	246
Atrial septal defect	186	42	..	..	144
Endocardial cushion defect	90	24	12	6	48
Patent ductus	210	.6	60	6	138
Coarctation of aorta	168	90	12	..	66
Tetralogy of Fallot	96	12	12	6	66
Aortic stenosis	96	..	..	..	96
Hypoplastic left heart	78	78	..	..	..
Endocardial fibroelastosis	60	6	18	24	12
Truncus arteriosus	42	36	..	..	6
Transposition of great arteries ...	66	18	30	6	12
Vascular ring	42	6	24	6	6
Single ventricle	18	..	12	..	6
Coronary abnormalities	30	12	12	6	..
Double outlet, right ventricle	24	..	6	12	6
Pulmonary atresia	30	6	24	..	..
Tricuspid atresia	30	12	12	..	6
Mitral regurgitation	18	..	..	6	12
Miscellaneous	144	36	36	18	54
TOTAL	2,520	468	300	120	1,632

Crippled Children Service Section of the State Department of Health in Sacramento for 1971, 1972 and 1973.[10,11] Each condition, however, was taken separately when it came to the mortality figures and a mean mortality figure for each condition was used in estimating operative mortality (see Table 7).

Most of the children who had ductus ligation would be lost to follow-up in the second decade and similarly 20 percent of children with surgically closed atrial septal defects. The rate of spontaneous closure of ductal ligation was likewise accounted for. This rate was 0.6 percent per annum after the age of 1 year.[12]

Table 8 lists in the first two columns the estimated incidence of congenital heart disease in live births for 1975.[3] Columns three through six list the estimated frequency of the eight groups of conditions for children born in 1975 at arbitrarily selected times. From these estimates it is possible to add total numbers of estimated cases of congenital heart disease in children born in 1975 who would be expected to live to 1994 and adding them to the total number of estimated cases of congenital heart disease in children born in 1976 who would live to 1994 (that is, in the 19th year). This procedure continued for all the year periods up to 1994. This gives the total number of expected congenital heart disease cases in 1994, namely 22,922.

In 1995 with a California population of more than 27 million a prevalence ratio can be estimated. Therefore with the assumption that the prevalence is relatively stable a total estimate for children with heart disease can be made for 1975 and a California population of just over 21 million (column seven, Table 8).

The maximum number of children with congenital heart disease who might be seen in 1975 is, therefore, 17,531. It is also possible to predict which types of lesions are in these children with congenital cardiovascular lesions (column seven, Table 8).

As an example of estimation of health care requirements the two commonest lesions have been selected, namely the ventricular septal defect and pulmonary stenosis. These two conditions together account for nearly half of the total number of estimated cases of congenital heart disease.

In 1975 there would be expected to be 810 children born with ventricular septal defects of which 36 percent[8] would probably be of at least moderate size (Table 9). On the basis of consultations with a pediatric cardiologist every two

TABLE 7.—*California Crippled Children Services Section Open Heart Surgery Figures* (Children 1-4, 5-20 years) From Which Mortality Estimates Were Derived (1971-1973)*[10,11]

	1971 (Percent)	1972 (Percent)	1973 (Percent)
59 Pulmonary stenosis	7	3	2
125 Atrial septal defect	1	1	1
41 Aortic stenosis	2	2	2
110 Tetralogy of Fallot	13	11	15
131 Ventricular septal defect	5	8	6
626 Total open heart cases	9	8	8

*These figures are derived from the 24 centers registered by the Crippled Children Services Program and do not reflect the mortality rates from the other 90 cardiac surgical centers in California.

TABLE 8.—*The Incidence, Frequency and Prevalence of Congenital Heart Disease in California*

The incidence is estimated for 1975, the frequency of congenital heart disease in 1976, 1978, 1984 and 1994 would be expected for those children born in 1975. The prevalence of congenital heart disease in 1975 is estimated.

	Incidence Among Live Births With Congenital Heart Disease in 1975		Expected Frequency for Selected Years				Expected Prevalence 1975	
	Number	Percent	1976 (Percent)	1978 (Percent)	1984 (Percent)	1994 (Percent)	Number	Percent
Ventricular septal defect	810	32	30	20	21	29	4,182	24
Pulmonary stenosis	282	11	17	21	28	30	4,003	23
Atrial septal defect	186	7	10	13	13.5	8	1,978	11
Aortic stenosis	96	4	6.5	8	11.5	16	1,637	9
Persistent ductus arteriosus	210	8	10	11	5	4	1,442	8
Coarctation of aorta	168	7	4.5	6	6	1	897	5
Tetralogy of Fallot	96	4	5	6	5	5	878	5
Miscellaneous	672	27	17	15	10	7	2,514	14
TOTAL NUMBERS*	2,520		1,460	1,147	849	587	17,531	

*Number of children with congenital heart disease who are expected to be born in 1975 and to survive to 1976, 1978, 1984 and 1994. The total number of predicted cases of congenital heart disease for 1975 is in the last column.

months for a year for this group and for the other 64 percent every four months, 3,300 visits might be anticipated. The children older than one year with ventricular septal defects are divided into five groups (after P. Wood)[9] and might be seen as follows:

Group I (a left to right shunt of 1.1 to 1.7:1) could be seen every two years and the remaining groups every six months. Group II (a left to right shunt between 1.8 and 2.9:1). Group III (a left to right shunt of over 3:1). Group IV (a left to right shunt between 1.5 and 3.5:1 and pulmonary hypertension) and group V (a left to right shunt of 0.5 to 1.5 and pulmonary hypertension).

In all, this would represent 7,770 patient visits to a cardiologist (Table 9).

From the group of children less than 1 year of age it is estimated that the majority of children with moderate shunts would be catheterized and about 20 would have a cardiac surgical procedure. From the over 1-year-old group (II and III) about 40 children per year would be expected to have corrective surgical operation and a similar number to have preoperative cardiac catheterizations.

Groups IV and V, children with a ventricular septal defect and pulmonary hypertension, have been prorated over the 20-year period and it is estimated that there would be about 25 catheterizations a year for each group and that the majority of group IV would have surgical operation (Table 9). Assuming a relatively stable surgery rate, there would be approximately 40 children in whom postoperative cardiac catheterizations would be required.

One patient visit each year for children with pulmonary stenosis and the assumption that 50 percent of the mild and all of the moderate and severe are eventually catheterized gives prorated estimates of 160 cardiac catheterizations per year and it is assumed that 50 percent of these children would have surgical operation (Table 9). In 1971, a total of 86 children had cardiac surgical operation on a stenotic pulmonary valve with approximately a 7 percent mortality.[10]

Discussion

There are both advantages and disadvantages in the use of the 20-year period 1975 through 1994 as opposed to the period 1956 through 1975 in the estimation of prevalence from incidence figures. Although by the use of this latter period, one can initiate the study with actual numbers of different types of congenital lesions, one is much less certain of attrition. Several major medical advances in the management of children were either perfected or first used between 1956 and 1975. Systemic to pulmonary anastomosis

TABLE 9.—*Estimated Health Care Requirements for Children in 1975 With Ventricular Septal Defect and Pulmonary Stenosis in California*

				Visits	*Catheterizations*	*Surgical Therapy*
Ventricular Septal Defect	4,182 cases					
Under 1 year[5]						
292 (36 percent)	Spontaneous closure			900	250	20
227 (28 percent)	Became smaller			700		
292 (36 percent)	Moderate size			1,800		
Over 1 year[9]						
1,382 (41 percent)	Group I	L to R	1.1-1.7:1	700		
775 (23 percent)	Group II	L to R	1.8-2.9:1	1,500	80*	40
135 (4 percent)	Group III	L to R	>3.0:1	270		
506 (15 percent)	Group IV	L to R	1.5-3.5:1 and pulmonary hypertension	1,000	25	25
573 (17 percent)	Group V	L to R	0.5-1.5:1 and pulmonary hypertension	1,000	25	
TOTAL 4,181				7,770	380	85
Pulmonary Stenosis	4,003 cases					
1,335	Mild					
1,334	Moderate					
1,334	Severe					
TOTAL 4,003				4,000	160†	80‡

*Includes 40 postoperative catheterizations per annum.
†On the basis of 50 percent of the mild pulmonary stenosis cases, all the moderate and severe will be catheterized over a 20-year period.
‡On the basis of 50 percent of the catheterization cases will have surgical operation.

was often lifesaving in situations of pulmonary oligemia. Open heart surgical operation to correct certain lesions became more practical. The mortality from transposition of the great arteries changed dramatically with the introduction of the balloon atrial septostomy (1966).

The importance of prevalence estimates of a disease process is evident when it is necessary to assess health care requirements. The health care requirements estimated in this study are probably overestimates as not all the cases will have been located and the attrition rate and surgical mortality may err on the conservative side.

The most recently available figures of the California Crippled Children Services pertaining to congenital heart disease were then compared with the estimates.

In the annual report of cardiac centers (1971 through 1973)[10,11] it is indicated that there were an average of 131 cardiac surgical closures of ventricular septal defects each year with a mortality of 6 percent in children under 21 years of age, figures similar to those estimated.

This report also indicates that just over 900 cardiac catheterizations were carried out in children under one year and 1,854 in children between 1 and 20 years of age. Although specific lesions are not commented upon, these figures would be compatible with the above estimates.

The assumptions made in this study probably err on the side of overestimating the population of specific congenital heart disease described in this study. It is to be reemphasized that the present estimates of the frequency of three conditions —persistent ductus arteriosus, bicuspid aortic valve and prolapsed mitral valve—are not accurate enough to be included in this study. However, this may in part be balanced by the genetic implications of increased survival of a group of patients with congenital heart disease.

It should also be noted that it is expected that the majority of children who have had cardiac surgical procedures will need to be studied further because of the high frequency of residua.[13,14]

Implications

Disease prevalence data are essential for the planning of health care delivery. The manpower and fiscal responsibilities can only be determined by a knowledge of the prevalence of disease process and the future predictions of the disease.

This paper describes an original method for determining prevalence estimates from incidence data. This method may be applied to any disease process which has a well-known natural history. Specifically, this paper predicts the amount of congenital heart disease in California for the next 20 years. It is important to realize that merely by increasing the estimates tenfold, the study is applicable to the whole of the United States.

Summary

In conclusion, this study has estimated the prevalence of congenital heart disease in California. To convert these estimates to apply to the whole of the United States of America, a population factor of ten times is required.

The study has outlined probable health care requirements for the two most common cardiac conditions which represent nearly 50 percent of the congenital cardiac lesions. Finally, this study may serve as a model on which prevalence estimates can be determined for future health care delivery.

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Specialty Conference

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Moderator
HAROLD J. C. SWAN, MD, PhD, FACP, FRCP *(London)*

Discussants
PETER T. MAGNUSSON, MD
NEIL A. BUCHBINDER, MD
JACK M. MATLOFF, MD
RICHARD J. GRAY, MD

An edited transcription of an Interdepartmental Clinical Case Conference arranged by the Department of Medicine of the UCLA School of Medicine (University of California, Los Angeles)

Aneurysm of the Cardiac Ventricle

Its Management by Medical and Surgical Intervention

Ventricular aneurysm is usually a complication of acute transmural myocardial infarction. The development of cardiac aneurysm represents a process of continued thinning and fibrosis of the necrotic tissue of the ventricular wall. Survival allows the development of a solid fibrous scar which of itself does not affect global ventricular function substantially. Hence, ventricular aneurysms can be present for up to 18 years without production of serious symptoms. The cases were reviewed of 45 patients in whom aneurysmectomy and myocardial revascularization were carried out. Surgical mortality was low (6.6 percent, 30 days); survival one year after operation was 76 percent, but at three years had fallen to 47 percent. Cause of late death was dominantly cardiac. In 19 patients postoperative study was done; although graft patency was observed in 98 percent, substantive improvement in ventricular performance was seen in a minority of patients. The outcome in patients with ventricular aneurysm is primarily related to the status of the residual myocardium and to the status of the vessels which supply it. The mechanism of clinical improvement after aneurysmectomy has not been clarified. However, the long-term results appear to be similar to those in patients with extensive myocardial infarction.

HAROLD J. C. SWAN, MD, PH D:* *A review of the literature on ventricular aneurysm indicates that it is a frequently occurring cardiac lesion,*[1] *that resection of aneurysm can be done with a low operative mortality*[2] *and that a significant proportion of patients improve clinically,*[3] *some in a spectacular manner. These reports fail to provide objective data about the natural history of established aneurysm without symptoms; nevertheless, the outlook for symptomatic patients seems to be poor.*[4-6] *The mechanism by which cardiac performance is improved after operation has not yet been determined, although the adverse mechanical*

*Department of Cardiology, Cedars-Sinai Medical Center, Los Angeles, and Department of Medicine, UCLA School of Medicine.

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Reprint requests to: H. J. C. Swan, MD, Department of Cardiology, Publication Office, Cedars-Sinai Medical Center, 8700 Beverly Blvd., Los Angeles, CA 90048.

consequences of paradoxical expansion[7] *and the favorable effect of reduction of ventricular volume on myocardial wall tension are frequently cited.*[8]

The purpose of this symposium is to review the significance and current management of this important complication of acute myocardial infarction, principally by a critical analysis of surgical material at the Cedars-Sinai Medical Center, Los Angeles. Among recent reports, we find that our experience is similar to that of Cooperman and associates[9] *and of Fisher and co-workers*[10] *with regard to two-year survival.*

Aneurysms of the cardiac ventricle are almost always a consequence of acute myocardial infarction. Of patients with acute myocardial infarction, in 4 percent to 15 percent ventricular aneurysm develops.[6,11] *Other causes, including coronary embolus, trauma, diverticulum or cyst, are relatively uncommon or rare. The aneurysm usually involves the ventricular apex, the anterior ventricle and septum, or the apex and anterolateral aspect of the left ventricle. Posterior aneurysms are uncommon and involve the left ventricle and at times the posterior ventricular septum and right ventricle. Aneurysms may be recognized or suspected during the acute infarction,*[12] *but are frequently first detected in the early or late convalescent phase of the illness on routine x-ray study of the chest by a characteristic distortion of the cardiac silhouette*[13] *associated with minor residual symptoms. Patients with aneurysm also present clinically with congestive heart failure or new angina, or both.*[1,9] *Ventricular arrhythmias intractable to antiarrhythmia treatment are less common forms of clinical presentation,*[14] *and systemic embolus is relatively uncommon.*

The formation of a cardiac aneurysm is related to the magnitude of involvement of ventricular myocardium during the acute episode. If the territory subserved by the affected artery is large, then transmural destruction is likely to occur. The specific anatomy of the diseased parent vessel and alternative (collateral) supply is important. Continued physical exertion or blood pressure elevation[12] *in the early phases of cardiac necrosis may predispose to aneurysm formation. Early steroid therapy may seriously impede the healing process and weaken the maturing scar tissue.*[15]

The effects of acute paradox on cardiac dynamics in early aneurysm[16] *and acute infarction*[17] *have been appreciated, but definite therapy based on such concepts has not yet been established.*

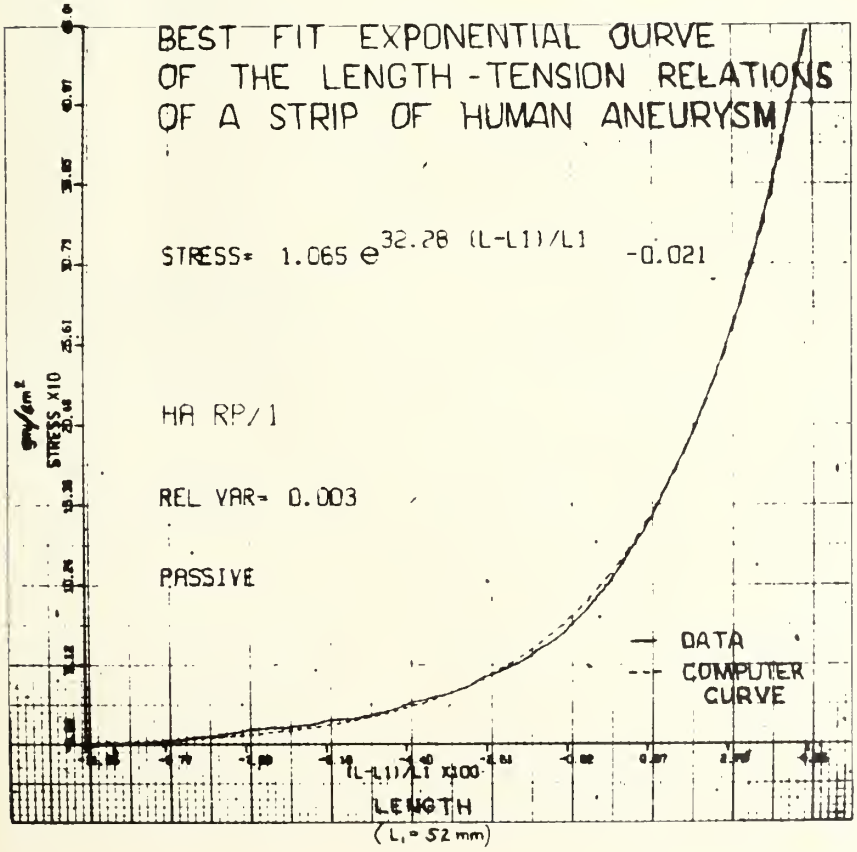

Figure 1.—Reproduction of the Calcomp Computer (Cal-comp Incorporated, Anaheim, California) printout, illustrating the length-tension data **(solid line)** of the aneurysmal strip and the best-fit exponential curve **(dashed line).** Stress is plotted on the vertical axis in grams per square centimeter, and length is normalized on the horizontal axis as a percentage of L_1 (length at 1 g of force). The exponential equation and its constants, and the computer identification of the data, are shown in the inset.

The current treatment of chronic aneurysm in the absence of symptoms is conservative, and it is usual to consider surgical measures only when symptoms appear. Such measures include excision with or without revascularization or, when necessary, replacement of the mitral valve.

Aneurysm may be defined by clinical, angiographic or anatomic criteria. As our present report relates primarily to aneurysms treated surgically, an anatomic description is in order. Thus, a chronic aneurysm usually consists of a discrete transmural scar of less than 0.5 cm thickness that may form a sacular bulge from the cardiac silhouette. A characteristic of such aneurysms is their tendency to collapse when the heart is emptied of blood at the beginning of open-heart surgical operation. This puckering inwards contrasts with the thicker-walled normal ventricular structure. The area of aneurysm tissue resected in our patients varied from 9 to 80 sq cm. The aneurysm consists of fibrous tissue with clusters of myocytes that frequently exhibit hypertrophy. Calcification, endocardial fibrosis and thrombus formation are relatively common. Acute or subacute aneurysms usually are made up of muscular and fibromuscular tissue.

Several clinical features may suggest ventricular aneurysm: abnormal left ventricular lift or heave, abnormal apex cardiogram,[12] *electrocardiogram*[18] *and echocardiogram.*[19] *For anterolateral aneurysm, the cardiac silhouette on an x-ray film of the chest*[13] *can be most dramatic. From an angiographic standpoint, segmental abnormality of ventricular wall motion, failure of change of shape or thickening, the presence of an avascular ventricular wall and diseased parent arteries are important.*[20]

Our experience during the period from January 1, 1972, to July 1, 1976, includes approximately 300 patients studied in the Cardiac Catheterization Laboratory and 65 patients operated on at the Cardiovascular Surgical Service of the Cedars-Sinai Medical Center, with an overall surgical mortality (30 days) of 6.6 percent. The current presentation is restricted to 45 surgical cases without ventricular septal perforation or mitral regurgitation for which full data (including preoperative catheterization and follow-up) were available. Preoperative and postoperative catheterization data were obtained in 19 patients.

Mechanical Effect of Ventricular Aneurysms

Parmley and colleagues[21] *studied the expansile nature of aneurysm tissue removed surgically from patients. The* in vitro *length-tension relation of this tissue was exponential (Figure 1). The speci-*

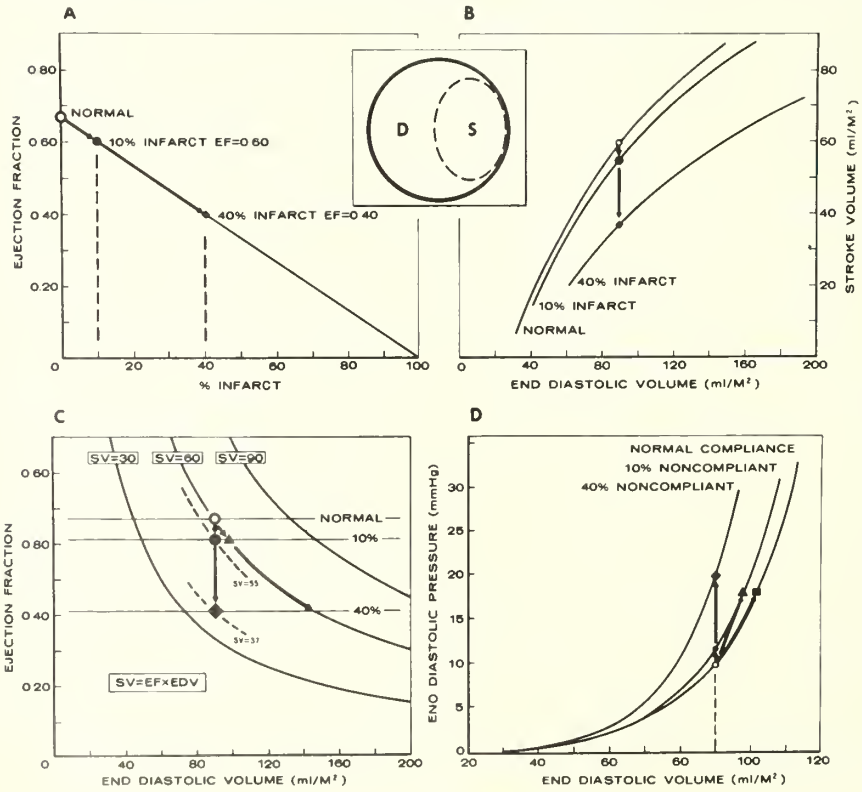

Figure 2.—Hemodynamics of a noncompliant infarct. **A.** Relationship of ejection fraction (EF), end-diastolic volume (EDV) and stroke volume (SV) to infarct size. The schematic diagram shows the heart in systole and diastole, and the infarct segment (delineated by the solid bars to the right of the inset) is assumed to be totally noncontractile and nondistensible. The resulting ejection fraction (EF) is a linear function of the remaining quantity of normally contracting myocardium. **B.** Left ventricular function curves are associated with reductions in ejection fraction (EF) and stroke volume (SV). **C.** The relationship between ejection fraction (EF), end-diastolic volume (EDV) and stroke volume (SV). When the ejection fraction is reduced by acute myocardial infarction, the result may be either a decreased stroke volume at an unchanged end-diastolic volume or a compensatory increase in end-diastolic volume to maintain stroke volume. **D.** The obligatory changes in the pressure-volume relationships consequent on a noncompliant infarct.

mens were identified histologically and in terms of time since the acute event. Established aneurysms (nine months or older) were usually composed of fibrous tissues that were extremely stiff and would only permit an increase of 1 percent to 4 percent in circumferential lengthening during systole. A few were fibromuscular—one permitted an increase of 10 percent. Early aneurysms (less than four weeks) were composed of muscular tissue and permitted a systolic increase of 25 percent in circumference. The presence of a compliant (and therefore expansile myocardial segment) would materially worsen the performance of a contracting sphere and would result in a lesser ejection fraction.

We had previously believed that a reduction in ejection fraction of the ventricle was an inverse function of the proportion of the ventricle involved in the infarction process (Figures 2 and 3).[17] *Compliance of the infarct has an additional adverse effect on ventricular mechanics. A noncompliant segment, however, would have little or no primary influence on performance apart from the loss of myocardial contractile elements. The findings of Parmley and associates*[21] *show that, for all practical purposes, chronic fibrous aneurysm is not significantly different from a rigid wall in terms of mechanics (Figure 4). In contrast, the early muscular aneurysm has an extreme depressant effect on overall performance, as indicated by a reduced ejection fraction. Global ventricular function is therefore adversely affected during the early phase after infarction and should improve with the formation of nondistensible scar tissue.*

Clinical Features of Established Ventricular Aneurysm

PETER T. MAGNUSON, MD:* The clinical presentation of the 45 patients considered in this report represents a spectrum of findings similar in distribution to that found in the general population of patients with symptomatic coronary artery disease, with some distinctive features.

The demographic and functional characteristics are important in that 43 of 45 (96 percent) of the patients are men, a higher proportion than reported in other major series. At the time of preoperative catheterization, the total population

*Department of Cardiology, Cedars-Sinai Medical Center, Los Angeles, and Department of Medicine, UCLA School of Medicine.

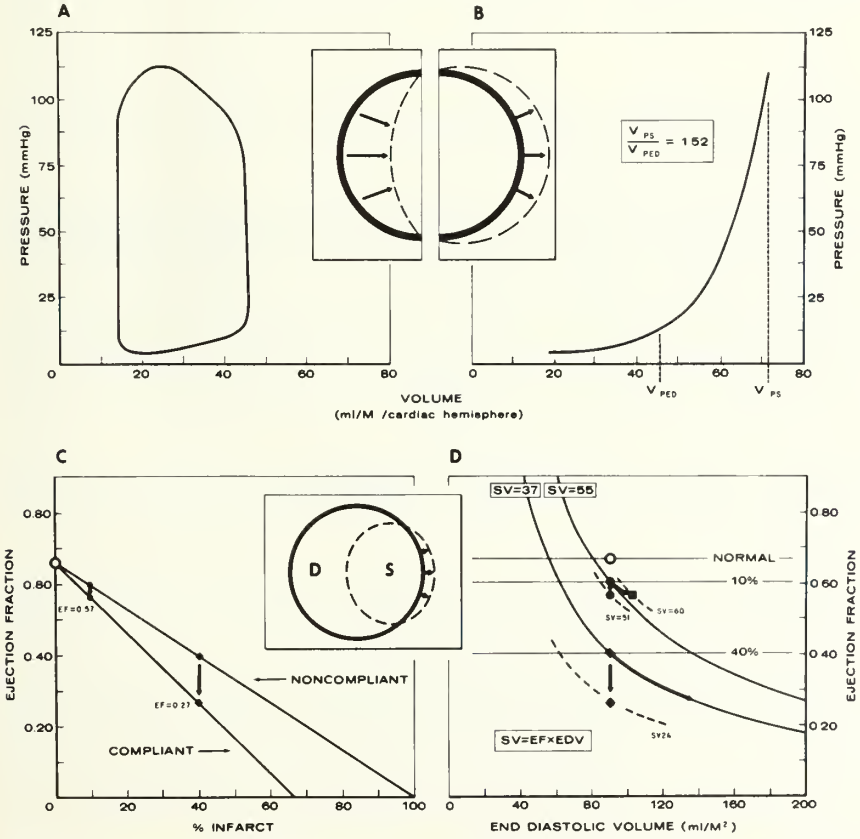

Figure 3.—Hemodynamics of a compliant infarct. **A.** Assuming that half of the spherical model is infarcted, the left ventricular pressure-volume relationship during systole and diastole in the noninfarcted cardiac hemisphere illustrates a normal pressure-volume loop and results in a ΔV (or stroke volume, SV) of 30 ml per sq meter. **B.** If the noncontractile infarct segment **(right panel)** shows normal compliance, it will stretch during ventricular systole according to its passive pressure-volume curve, with resultant paradoxical expansion. Forward stroke volume can be maintained only with an increased end-diastolic and a reduced peak systolic pressure. **C.** Effect of normal compliance characteristics with paradoxical pulsations on ejection fraction (EF). The ejection fraction will be further reduced in the presence of a compliant infarct segment (circles for 10 percent infarct, diamonds for 40 percent infarct). **D.** Interrelationship of ejection fraction (EF), stroke volume (SV) and end-diastolic volume (EDV). In the presence of paradoxical pulsation, reduction in ejection fraction is associated with a decrease in sroke volume exceeding that predicted for a noncompliant infarct as shown in Figure 2A. When end-diastolic volume remains unchanged in the presence of normal overall ventricular compliance, left ventricular end-diastolic pressure is also unchanged **(Figure 2D, open circle).** The stroke volume value of 51 shown here in D may be returned to normal levels by compensatory dilatation only if the infarct is small (10 percent infarct). This rise in end-diastolic volume produces a concomitant rise in left ventricular end-diastolic pressure **(Figure 2D, square symbol).**

had a mean age of 55 years, ranging from 32 to 72 years. Most of the patients (81 percent) were in functional classes III and IV, as might be expected in patients referred for surgical intervention.

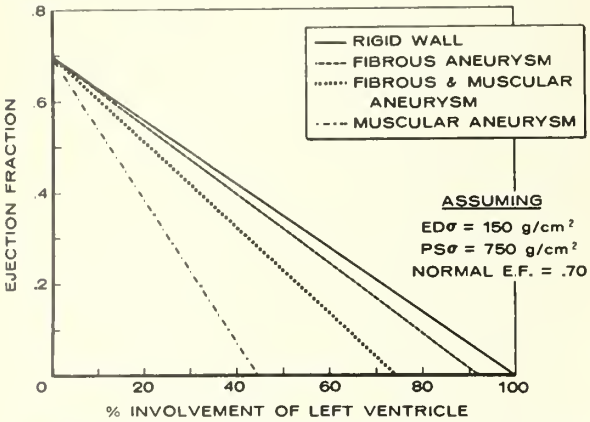

Figure 4.—Theoretical calculation of ejection fraction (vertical axis) in patients with aneurysms of different size and stiffness. The relative size of the aneurysm (percentage of involvement of the left ventricle) is indicated on the horizontal axis. For comparative purposes, the data have been calculated assuming an end-diastolic stress (EDσ) of 150 grams per sq cm and a peak systolic stress (PSσ) of 750 grams per sq cm. If the area of the infarct is initially noncontractile and nondistensible, the ejection fraction will then be reduced in direct relation to the proportion of inert elements (solid line). When the compliance characteristics of the infarct are considered, it is apparent that there will be outward movement of the infarct segment during each systole. Therefore, a portion of the potential systemic stroke volume will be delivered into this segment and the ejection fraction will be further reduced. The theoretical reduction in ejection fraction produced by each of the three types of aneurysms studied is plotted.

Of the patients, 75 percent had a history of angina. Nevertheless, in contrast to other patients with coronary artery disease referred to us, 51 percent of the patients had symptoms compatible with congestive heart failure; the combination of angina and symptoms of heart failure was present in slightly more than a third of the patient population.

Serious ventricular arrhythmias (ventricular tachycardia and ventricular fibrillation) were present in 20 percent of the patients and were the predominant presenting feature in six of these nine patients. In four additional patients, ventricular fibrillation had occurred during myocardial infarction. Systemic embolization had occurred in only two of the patients; this was a surprisingly low figure inasmuch as anticoagulation was carried out in only a third of the patients and a high incidence of mural thrombi was present at preoperative catheterization.

Regarding infarct location, 87 percent of the patients had antecedent anterior or lateral wall myocardial infarction, implicating the anterior descending coronary artery and its major branches. The primary indication for catheterization, and in large part for subsequent surgical operation, was slanted heavily toward those patients with angina as an important symptom. In

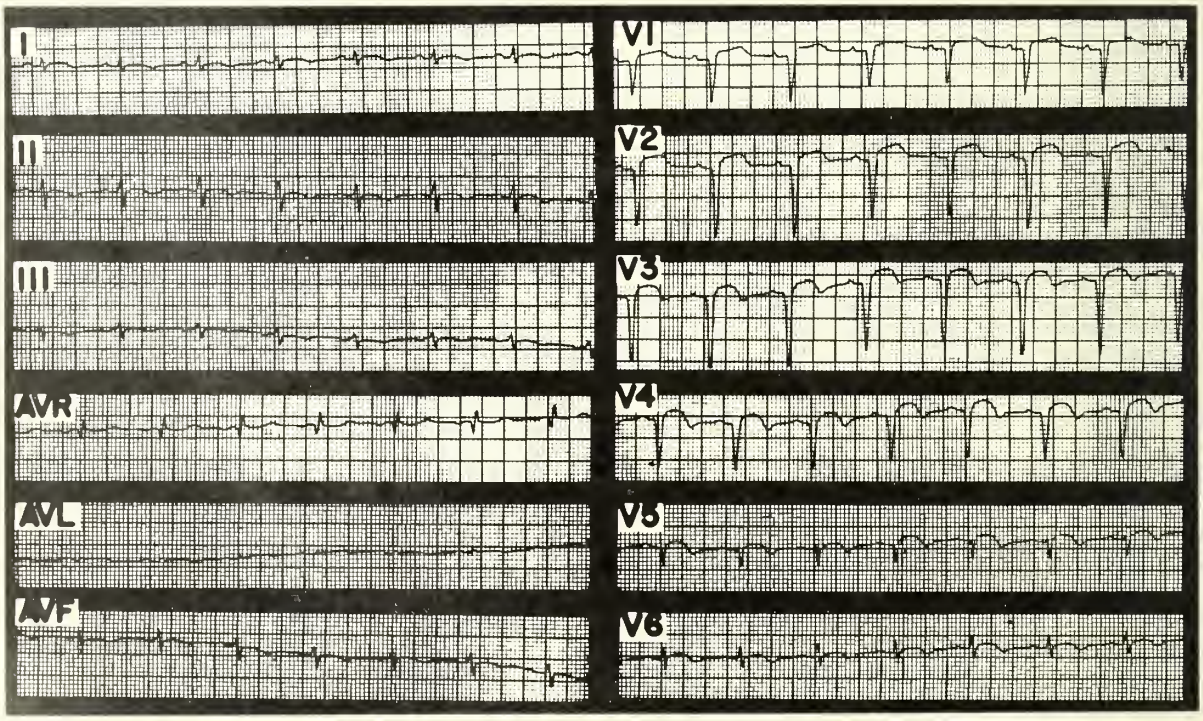

Figure 5.—The "classical" electrocardiogram of anterior ventricular aneurysm with R wave absence from V1 through V5 and elevated coved ST segments in the anterior precordium. This is not a universal finding in ventricular aneurysm of the anterior wall.

contrast to the older published reports, only a few patients were referred *solely* because of significant heart failure, although about half of the total group did have symptoms of heart failure. Life-threatening ventricular arrhythmia not controlled with intensive pharmacologic regimens was the sole indication for referral in seven patients. Studies were also done in those in whom ventricular aneurysm was strongly suspected based on findings from clinical examination, in those in whom there were notably abnormal findings on treadmill examinations and in patients surviving massive myocardial infarction.

The classical electrocardiographic evidence (Figure 5) for ventricular aneurysm was present in only 65 percent of the group; this was similar to that reported in patients with aneurysm defined by ventriculography.[18] A subgroup of 34 patients was identified in which the causative infarction could be clearly related to the time of referral for catheterization. Of the patients, 75 percent presented for catheterization within one year after infarction. Those patients presenting less than three months after their infarction had clinical findings equally divided between those with angina and those with ventricular arrhythmias. Patients studied at 3 to 12 months after infarction were predominantly those with angina and included all three of the patients referred solely because of heart failure. Those patients presenting one year after infarction were all referred because of unstable or incapacitating angina.

Coronary Anatomy and Left Ventricular Function

NEIL A. BUCHBINDER, MD:* Each of the 45 patients underwent left heart catheterization with left ventriculography and selective coronary angiography. In 30 patients right heart catheterization was also done with determination of cardiac output by the indicator dilution method. The angiographic and hemodynamic data were reviewed and recorded according to the format recommended by the American Heart Association (Figures 6 and 7).[22]

The maximal degree of narrowing was determined for each of the 15 segments of the coronary arterial tree. In the left anterior descending coronary artery, the proximal segment was defined as that portion upstream to the first septal perforating branch, and the distal was defined as that portion after the first septal perforator. The systolic motion of each segment of the left ventricle was determined and recorded as being either hypokinetic, akinetic or moving in a paradoxical (dyskinetic) fashion. Segments exhibiting both akinesia and dyskinesia were included as aneurysmal when clearly delineated from surrounding myocardium.

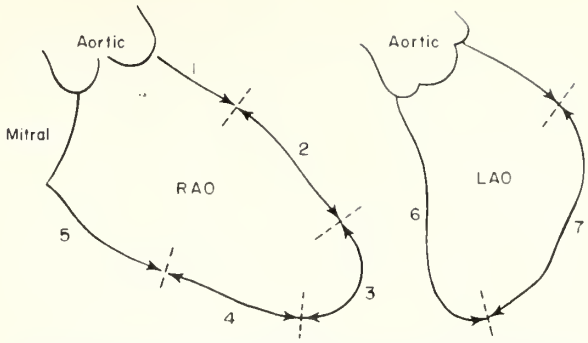

Figure 6.—Regional division of the left ventricular wall as defined by right anterior oblique (RAO) **(left panel)** and left anterior oblique (LAO) **(right panel)** ventriculograms. The location of areas of hypokinesis, akinesis or dyskinesis was defined in our cases in accordance with this format.

Anatomic Findings

The apical segment was the most frequently involved, being abnormal in 93 percent of the patients. The next most frequently involved was segment 2 (the midanterior wall), which was abnormal in 82 percent. The inferior apical segment (segment 4) was involved in 42 percent of the patients, and the septal segment (number 6), was involved in 24 percent. These segments (numbers 2, 3, 4 and 6) usually receive their blood supply from the regions of the left anterior descending coronary artery. Segment number 5, supplied by the right coronary artery, was the least commonly involved segment and was sometimes involved in combination with segment 4. Segments 1 and 7 were not involved by aneurysm in any of the patients studied. In four patients only one ventricular segment was involved. In only six patients were four or more segments involved by aneurysm. An almost equal number of patients had 2-segment or 3-segment involvement. Altogether, this group made up almost 80 percent of the patients studied.

If coronary disease is defined as greater than 50 percent narrowing of the diameter of the parent vessel, then 67 percent of the patients had triple vessel disease, 27 percent double and 6 percent single vessel disease. Considering lesions of greater than 90 percent as representing significant

*Department of Cardiology, Cedars-Sinai Medical Center, Los Angeles, and Department of Medicine, UCLA School of Medicine.

stenoses, 9 percent of patients had each of the three vessels narrowed by 91 percent to 100 percent while 31 percent had double, and 56 percent single vessel disease.

Relation of Coronary Anatomy to Aneurysm Location

Although aneurysms can be related to the distribution of only one major coronary vessel, the overall extent of the coronary disease is substantially greater, most of the patients having serious disease of at least one additional vessel. In 56 percent of the patients, the vessel that supplied the area of the aneurysmal segment was completely occluded. In 27 percent, the diameter was narrowed by 91 percent and 99 percent, and in only 15 percent was it less than 90 percent. We cannot exclude the possibility that a vessel was completely occluded at the time of the acute myocardial infarction and subsequently became recanalized.

Of the patients, 41 (91 percent) had aneurysms in the distribution of the left anterior descending coronary system with involvement of the anterior wall, apex or septal portions of the ventricle, or combinations of these. Although 30 of the patients (73 percent) had the site of maximal narrowing proximal to the first septal perforating branch of the anterior descending coronary artery, 27 percent of the patients had narrowing distal to the first septal perforator. This shows that disease distal to the first septal perforator can account for substantial myocardial involvement and subsequent myocardial destruction. In certain patients with similar coronary lesions the presence of preexisting collateral vessels may protect against the development of aneurysms.

Hemodynamic Findings

Pertinent hemodynamic measures in the 45 patients are shown in Figure 8. The average cardiac index and peak dp/dt for the group remained within normal limits; the average end-diastolic pressure, although elevated, was only moderately so. Nevertheless, the average end-diastolic and end-systolic volumes were increased significantly (122 ml per sq meter and 82 ml per sq meter, respectively), and the average ejection fraction at 0.33 was reduced. More impressive, however, was the wide range of values in each of the categories, indicating that function depended on factors other than the presence or extent of aneurysm, that is, on performance of residual myocardium.

Preangiographic symptoms correlated poorly with the measurements described. A history of

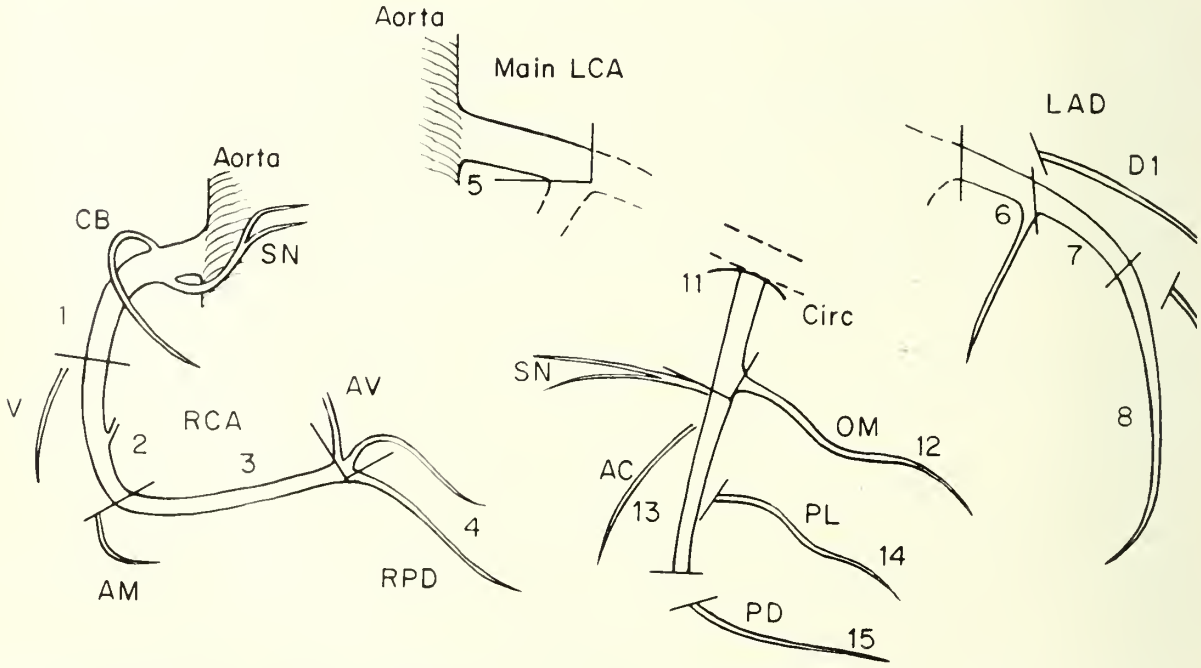

Figure 7.—Classification of the coronary arterial tree for the purposes of categorization and localization of coronary arterial obstructive lesions. AC = atrial circumflex; AM = acute marginal; AV = artery to A-V node; CB = conus branch; Circ = left circumflex artery; D1 = first diagonal; LAD = left anterior descending coronary artery; LCA = left coronary artery; OM = obtuse marginal; PD = posterior descending; PL = posterolateral; RCA = right coronary artery; RPD = right posterior descending; SN = sinus node; V = ventricular branch.

congestive heart failure was consistently present only in patients with the highest left ventricular end-diastolic pressure and the lowest cardiac output and left ventricular dp/dt. With the exception of this isolated group of five patients, we could not correlate preoperative congestive heart failure to any of the hemodynamic measurements. Furthermore, although patients with four or more involved segments seemed to have abnormal hemodynamic findings, this was not statistically significant.

Segmental Performance

Various angiographic definitions of aneurysms have been reported in the literature; some studies including only dyskinetic areas, and others combining akinetic and dyskinetic segments. Our patients were classified as having akinetic or dyskinetic segments. Patients with dyskinetic and akinetic segments, and those whose aneurysms were only dyskinetic could not be separated on the basis of any of these hemodynamic measurements. We concluded that the diagnosis of aneurysm is not confined to persons with dyskinetic segments only. Furthermore, in the *nonacute* stage, no difference in hemodynamic behavior in each of these types of segmental dysfunction could be shown.

Diastolic Ventricular Contour

We reviewed the end-diastolic ventricular contour in each of our patients. Figure 9 shows diagramatic representations of various diastolic left ventricular configurations as seen in a right anterior oblique ventriculogram. In many forms of heart disease the ventricle assumes a more globular appearance in contrast to the partial ellipsoid of the normal diastolic ventricle. This globular appearance can be seen in cardiomyopathies, long-standing valvular regurgitation with myocardial changes, as well as in ischemic heart disease. The presence of a distinct diastolic bulge associated with wall thinning, as well as that of an apical cutoff caused by mural thrombus, is considered highly suggestive, if not pathognomonic,

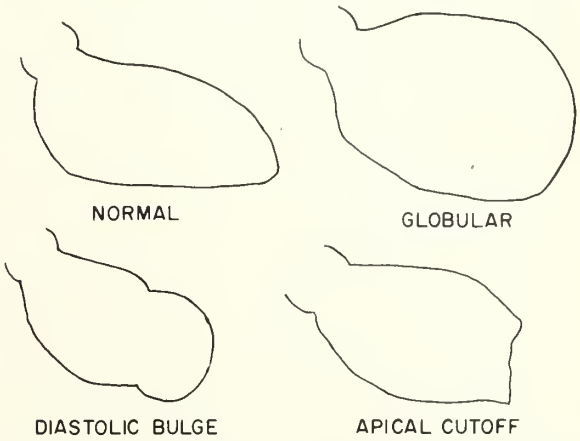

Figure 9.—Line drawings of representative diastolic contours selected from our patients with surgically proved ventricular aneurysm. The cardiac silhouette may be normal, globular, or may show the classical diastolic bulge or apical cutoff. Note: The more classical finding of aneurysm was found in less than 50 percent of our patients.

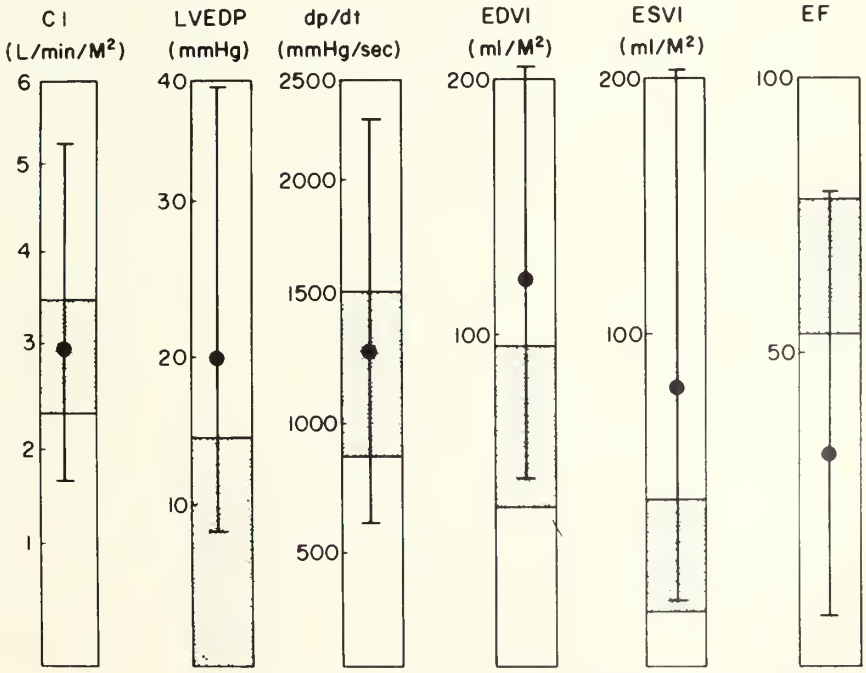

Figure 8.—Average and range of cardiac index (CI), left ventricular end-diastolic pressure (LVEDP), maximal dp/dt, end-diastolic volume index (EDVI), end-systolic volume index (ESVI) and ejection fraction (EF) in 45 patients with ventricular aneurysm. The stippled areas show the range accepted as normal for our laboratory. The solid dots and the bars indicate the average and extreme values of data obtained in these patients (see text).

of a ventricular aneurysm. In 40 percent of our patients one of the latter two configurations considered diagnostic of a ventricular aneurysm was seen. In the remaining 60 percent of patients, however, ventricular contours were relatively normal or tended toward a globular pattern, as also reported by Raphael and co-workers.[20]

Mural Thrombus

The preoperative diagnosis of mural thrombus was assessed by comparison with findings at operation. Angiographically, thrombus was thought to be present in ten of the 24 patients in whom it was later found at surgical inspection. In only one of 18 patients without thrombus did the angiogram suggest its presence. From this observation we can conclude that an angiographic appearance suggestive of mural thrombus is reasonably specific but somewhat insensitive.

Surgical Treatment and Intraoperative Management

Indications for Surgical Operation and Intraoperative Considerations

JACK M. MATLOFF, MD:* The decision to recommend surgical therapy for heart disease should be predicated on the surgeon's ability to improve a patient's symptomatic or functional status, or both, and on the longevity relative to his prognosis without operation. In considering left ventricular aneurysms, this decision can be a difficult one, inasmuch as the prognostic significance of an aneurysm or large dyskinetic area has not yet been clearly defined. Notwithstanding, the classic study of Schlichter and associates[6] showed that the three-year survival after the diagnosis of aneurysm was approximately 25 percent. Although improved medical management of congestive heart failure has been developed since their report in 1954, our ability to treat coincident ischemia has not improved as dramatically. It is therefore not surprising that a report in 1974 by Nagle and Williams[5] showed that the three-year survival after the diagnosis of aneurysm still remained 25 percent 20 years later. Furthermore, in 1972 Davis and Ebert,[4] reporting on a clinical-pathologic correlation of 40 patients with aneurysms, found that no patient in their study was asymptomatic and that the average survival after diagnosis was 3.9 years, with a range from two weeks to 12 years. These reports may be taken as a baseline against which surgical therapy can be evaluated.

One further concept should be presented in relation to consideration of surgical therapy for patients with aneurysms. In the absence of a mechanical defect, the ischemic effects of obstructive coronary atherosclerosis can generally be conceived as describing a continuum from chronic to acute, asymptomatic or stable, or both, to symptomatic. The state of a patient at a given time is an expression of variable physiologic events imposed on a relatively stable anatomic substrate. In the presence of a mechanical defect, such as ventricular septal defect, mitral regurgitation or ventricular aneurysm, the relatively stable anatomic substrate may in itself become the primary determinant of the physiologic and clinical state of the patient. Therefore, considerations of therapy may be determined as much by the presence of the mechanical defect as of the underlying coronary anatomy.

Indications for Surgical Therapy

Patients with left ventricular aneurysms can present with acute or chronic symptoms, which determine whether surgical operation is urgently or electively indicated. I would like to focus initially on the *urgent indications.*

In the literature, the four-month period after the infarction that results in aneurysm formation seems to be critical and corresponds to the time required for maturation of the fibrous tissue that makes up a chronic aneurysm. It is within this period that urgent decisions relative to surgical therapy are experienced.

Perhaps the most acute example of functional (as opposed to structural) aneurysm is that which occurs during extreme ischemia, involving a large proportion of the ventricular myocardium before actual infarction. As this is a potentially reversible situation, it is an opportunity for the surgeon to apply prophylactic therapy by early revascularization. This situation is epitomized in patients with preinfarction angina and high grade lesions in the proximal coronary arteries.

As mentioned previously, there are significant hemodynamic consequences of an acute aneurysm (3 to 30 days after infarction) when, before the laying down of fibrous tissue, the elasticity coefficient is greatest and true paradox occurs. In this circumstance, aneurysmectomy in the form of acute infarctectomy has been recommended.

*Department of Thoracic, Cardiac and Vascular Surgery, Cedars-Sinai Medical Center, Los Angeles, and UCLA School of Medicine.

We do not feel that at present this is an appropriate indication for surgical therapy. Such patients in low output states may be managed successfully with impedance reduction. They frequently have extensive additional vascular disease and angiography may be delayed and revascularization carried out three to four weeks after infarction.

As for the potential for rupture, such a threat is not a bona fide indication for aneurysmectomy unless an acute infarction or reinfarction occurs in contiguity with chronic aneurysm. If the rupture of the myocardium occurs during an acute infarction—often under circumstances such as severe effort, uncontrolled hypertension or concomitant steroid therapy—this results in false or pseudoaneurysm formation.

With regard to *elective (late) indications,* uncontrollable congestive heart failure, with or without angina pectoris, has been the classic indication for surgical therapy of aneurysms. Although medical therapy for the control of congestive heart failure has improved, control of ischemia due to disease in other coronary arteries in adjacent, noninfarcted segments is difficult to achieve. Beta-blockade is poorly tolerated, or not tolerated at all, and impedance reduction has limits to its effectiveness.

Alterations of the physical dimensions of the left ventricle, loss of functional muscle mass from the antecedent infarction, continued ischemia in the viable myocardium and the coexistence of associated mechanical defects (specifically ventricular septal defect and mitral regurgitation) may together be excessive burdens for the heart to carry. In such circumstances, medical therapy has not been very effective. Theoretically, surgical therapy encompassing revascularization and correction of mechanical defects should offer beneficial effects. On the other hand, if true ischemic myocardiopathy is an important underlying factor in some patients, then only partial improvement can be expected from surgical therapy.

Recurrent or persistent angina pectoris is the other primary symptom that frequently leads to a surgical evaluation of the patient with an aneurysm. Whether related to the hemodynamic burdens that increase oxygen demand or to coexisting obstructive lesions in other vessels, this symptom is almost always eliminated or improved by saphenous vein bypass.

Although life-threatening ventricular arrhythmias occur frequently in association with aneurysms, they rarely fail to respond to pharmacologic therapy and therefore constitute an uncommon primary indication for surgical therapy. Unfortunately, the mechanism by which these occur has not been elucidated. Routine electrographic mapping of the ventricle in the operating room would help to define the mechanism involved in the production of such arrhythmias and probably would contribute to the efficacy of excision therapy.

Recurrent peripheral arterial embolism is the least commonly encountered primary indication for surgical therapy. Considering the frequency and extent to which blood clot is found within the ventricle, the rare occurrence of embolism is surprising; anticoagulant therapy does not seem to influence its incidence.

Intraoperative Considerations

All of our patients with aneurysm are operated upon on total cardiopulmonary bypass, using normothermia, hemodilution to hematocrits of 22 percent to 25 percent, and disposable bubble oxygenators. A left ventricular sump is introduced, via the right superior pulmonary vein, across the mitral valve to the left ventricle to achieve a dry field and to help delineate the margins of the aneurysm. Aortic cross-clamping with induced ventricular fibrillation is used to minimize the chances for occurrence of embolism before any manipulation of the heart. Myocardial preservation is of paramount importance, and ischemic intervals are limited to ten minutes. With the midportion of the aneurysm incised, existing thrombus is removed, the papillary muscles are carefully examined, and the state of scarring of the septum and endocardium ascertained. The aneurysm is resected to within 0.5 cm of viable muscle, carefully avoiding the papillary muscles and septum if possible. If a ventricular septal defect is present, it is then closed. At this point, distal coronary anastomoses are carried out, always using saphenous vein and a 6-0 interrupted silk technique. Once these procedures are completed, attention can be turned to problems of the mitral valve. We believe that annuloplasty has no role in the treatment of mitral regurgitation due to ischemic heart disease, and that mitral valve replacement through the ventriculotomy is appropriate. At present, we use the Hancock

Porcine Bioprosthesis (Hancock Laboratories, Santa Ana, California) for this purpose. At this point the ventriculotomy is closed with interrupted mattress sutures through long Teflon® felt bolsters, and the everted margins are oversewn with a second suture line. The patient is left on total bypass to support the heart and maximize recovery from the earlier ischemic insults; the proximal anastomoses are accomplished over a partially occluding aortic clamp.

If problems occur after discontinuing bypass, we prefer to use pharmacologic means of support. In three of the cases reported here, an intraaortic ballon was also used; in one instance the balloon was in place before operation. When extreme hemodynamic problems occur, we have found that direct left ventricular pressure monitoring has been most helpful. Finally, in the presence of arrhythmias, atrial or atrioventricular sequential pacing has been used by insertion of temporary atrial and ventricular pacing wires before closure.

Of the technical considerations that remain to be resolved, the following continue to be matters for concern: (1) How best can the non-infarcted myocardium be protected? (2) Should all chronic aneurysms be excised (and, if so, when) and in which instances should bypass of diseased vessels alone be employed? (3) When should the mitral valve be replaced? (It has long been an issue of concern as to why the mitral valve is not involved more often.) (4) How much ventricle should be resected, particularly in relation to the occurrence of preoperative arrhythmias and in relation to residual ventricular volume? (5) How is intracavitary clot best managed in a patient with an akinetic segment composed of admixed viable muscle and fibrous tissue?

Clinical Results of Aneurysmectomy

RICHARD J. GRAY, MD:* In all our patients concomitant aortocoronary bypass graft was carried out; an average of 2.0 grafts per patient were done. Perioperative mortality was 6.6 percent and included one operating room death and two patients who died within 30 days. Surviving patients were seen by us six weeks after the operation, then at six-month intervals for two years, and yearly thereafter, in addition to visits to their referring physician, usually an internist or cardiologist. Long-term follow-up information was obtained by telephone when patients had moved away from the local area. The cases of 45 patients are reported, representing a total of 1,522 patient months with a maximal follow-up of 63 months; the mean period of follow-up is 33 months.

The current survivors are alive at a mean of 26 months after surgical operation. Those surviving 30 days or more, but who subsequently died during this review period, had lived for an average of 17 months after their operation. Of our total mortality, 8 of 18 (44 percent) patients died during the first postoperative year. The likelihood of being alive one year after operation was 76 percent, and at three years, 47 percent. The cause of death was cardiac in 13, noncardiac in 3 and unknown in 2. In those dying within one year, cardiac deaths tended to predominate. Noncardiac deaths in those dying after one year included cerebral vascular accident (one), hepatoma (one) and suicide (one).

There were 39 patients for whom accurate functional state was available or had been determined before a late death. The functional state was good with minimum or no symptoms in 28 (70 percent), adequately functional with moderate symptoms in 4 (10 percent), while 7 (18 percent) were quite symptomatic and functional, class IV. Of 42 patients whose employment status could be determined, 50 percent have or had returned to full or part-time employment, 31 percent are able to work and seeking employment. Nineteen percent of those under age 50 are not working for health or personal reasons.

Attempts to predict the likelihood of dying within one year, or, alternately, to predict the likelihood of surviving for one year or more, were not successful when age, cardiac index, end-diastolic volume, left ventricular end-diastolic pressure, ejection fraction or amount of removed tissue were examined. In contrast, Cooperman and co-workers[9] found that age above 60 years, severe congestive failure and low cardiac output correlated with mortality.

Our patients were classified into two groups, group I (dying within one year of cardiac causes, a total of 7), and group II (those surviving more than one year or dying later than 12 months of noncardiac causes, a total of 27). Only cardiac index was statistically different in the two groups. The likelihood of survival longer than 12 months could not be predicted when the number of

*Department of Cardiology, Cedars-Sinai Medical Center, Los Angeles, and Department of Medicine, UCLA School of Medicine.

asynergic segments involved, adequacy of revascularization or time from acute myocardial infarction were assessed.

The outcome was then examined with regard to presenting symptoms. Patients with severe angina with or without mild congestive heart failure were much more likely to fall into group II (total, 20) than group I (total, 3), suggesting that they were more likely to do well than poorly. Those presenting with severe congestive heart failure with or without mild angina fell more equally into group I (total, 3) and into group II (total, 5).

In patients presenting with either congestive heart failure or angina, or both, 24 were judged to be improved symptomatically after surgical therapy. Of these 24 patients, there were 21 whose preoperative symptom was severe angina. In seven patients operation was carried out primarily because of life-threatening ventricular arrhythmias. This group of seven contained the three perioperative mortalities; the remaining four patients, however, did well and were judged improved after operation.

Most of our patients (93 percent) survived surgical operation, left the hospital and showed improvement for at least several months. Nevertheless, many patients did not survive beyond the first year or symptoms redeveloped late after operation. As in the recent reports of Cooperman and colleagues[9] and Fisher and associates,[10] clear-cut prediction of poor outcome failed when age and various standard hemodynamic and ventriculographic measurements were used.

Patients presenting with signs of continued myocardial ischemia associated with surgically correctable coronary disease and ventricular aneurysm are those whose course is most favorable. Least predictable are patients with severe congestive heart failure. However, since a few patients in this category showed dramatic clinical improvement, these patients should also be considered for surgical therapy. They have a particularly poor prognosis when managed only medically.

Postoperative Catheterization

Dr. Buchbinder: Of the 19 patients in whom postoperative cardiac catheterization was carried out (Figures 10 and 11), studies were done early (two to nine weeks) in 11 to define the prognostic implications of surgical operation, and studies were done late (more than six months) in 8 because symptoms had recurred or failed to disappear. Of those eight patients, five had heart failure, two had angina, and 1 both angina and

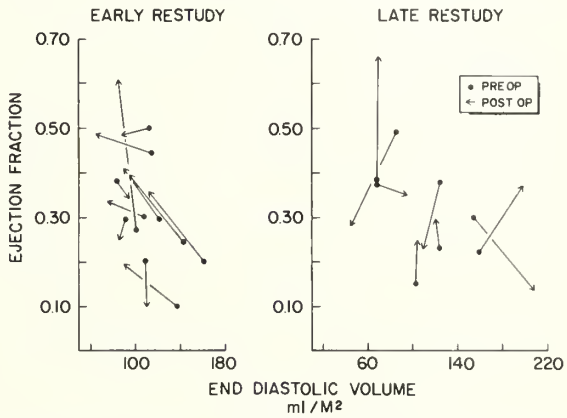

Figure 11.—The relation of ejection fraction to end-diastolic volume index in patients who had aneurysmectomy and myocardial revascularization. In most of the early restudies there was the expected reduction in end-diastolic volume associated with an increase in ejection fraction. However, in the patients (symptomatic) in whom late restudy was done, there was a variable change, including several examples of significant deterioration. In both the early and late restudy groups there were patients in whom was found the desired favorable response of a decrease in end-diastolic volume and an increase in ejection fraction.

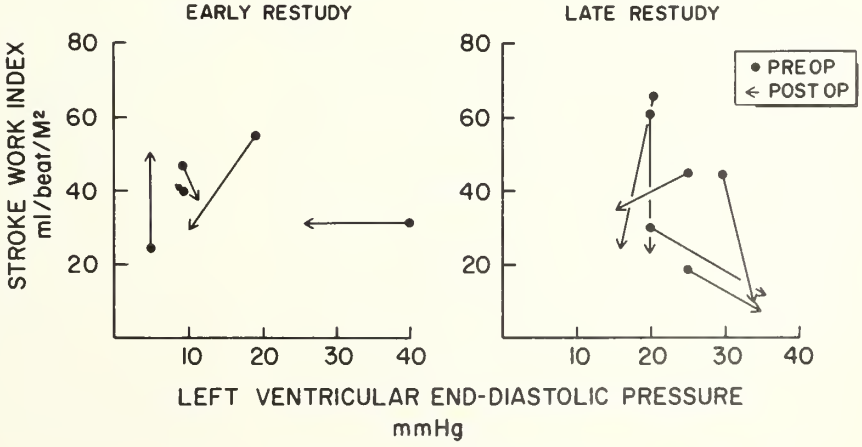

Figure 10.—The relation of stroke work index to left ventricular end-diastolic pressure in two groups of patients studied before and after resection of ventricular aneurysm and myocardial revascularization. In the patients in whom early restudy was done, there was a return of end-diastolic pressure toward normal but no consistent alterations in sroke work index. In the late restudies (symptomatic) there was a consistent reduction in stroke work index, and in several an increase in end-diastolic pressure (see text).

failure. When reexamined, 38 of 39 implanted grafts were patent (98 percent). However, two of these grafts, although patent, showed narrowing in the native circulation distal to the graft insertion. In the 11 patients in whom early studies were done, the average stroke volume index was identical in the preoperative and postoperative studies. The left ventricular end-diastolic pressure dropped from 21 to 16, and the peak dp/dt was essentially unchanged. The end-diastolic volume was diminished while the ejection fraction increased. In only one patient was hemodynamic function notably improved, with the stroke volume index almost doubling. From these data, as in the report of Fisher and co-workers,[10] it would seem that in these patients early hemodynamic improvement occurred to only a mild or moderate degree. Furthermore, two of these patients had mitral regurgitation, not present to the same degree in the preoperative study. In one patient, regurgitation was severe; in the other it was moderate. Three of these 11 patients subsequently died of cardiac causes: one of acute myocardial infarction 21 months after the operation; another 6 months postoperatively; the third patient died suddenly more than three years after the operation. The remaining eight patients did well from the cardiac standpoint, although three died of noncardiac causes a year and a half to five years after the operation.

The eight patients in whom studies were done because of the development of cardiac symptoms six months to a year after operation had a different hemodynamic pattern. In these patients the stroke volume index was found to be decreased in the postoperative study, the left ventricular end-diastolic pressure was substantially increased, the peak dp/dt dramatically decreased and the end-diastolic volume increased, while the ejection fraction remained the same. Six of the patients had recurrent congestive heart failure. Mitral regurgitation, more severe than in the preoperative study, was present in each of the six patients. In two patients, mitral regurgitation was graded as severe, and in four it was moderate. In only one of the six patients with mitral regurgitation was a new causative factor identified. In that patient, an occluded right coronary artery graft resulted in an inferior wall infarct and papillary muscle dysfunction. In the remaining patients, either subclinical myocardial damage occurred or the operative procedure distorted the mitral apparatus causing the mitral regurgitation. In addition to the mitral regurgitation, three of the patients with failure had an increase in ventricular asynergy.

Three patients in whom late studies were done had recurrent angina. The cause was progression of native coronary disease in one patient, incomplete revascularization in the second patient and graft occlusion in the third. From these data it would appear that initial early hemodynamic measurements show a moderate improvement in patients undergoing combined revascularization and aneurysmectomy. The data also suggest that increasing postoperative mitral regurgitation may be a major consequence of aneurysmectomy. Recurrence of angina seems to be related either to incomplete revascularization or graft failure or progression of native coronary disease.

Concluding Comments

Dr. Swan: *Basic physiologic evidence supported by experimental studies indicate that the principal adverse mechanical effect of major infarction occurs in the acute phase when true dyskinesis exists and the potential for a creep or stretch effect of the infarcted area is greatest. The delicate connective tissue elements of the myocardial cells and intercellular structures are not supported by the sustaining contraction of the myocardial sarcomeres, and all systolic forces generated by the remaining myocardium are borne by myocardial connective tissue. It would seem that aneurysm development closely relates in time to an acute infarction, although its recognition may be delayed more than a decade.*[4]

In order to minimize the stretch effect, the concept of impedance reduction has theoretical benefit; it would appear that this approach should be studied in extensive infarction so as to prevent the occurrence of a large aneurysm and make the consolidation of a tight scar of the smallest possible magnitude more likely. Although excision of acute infarcts of moderate size can be achieved with acceptable operable risk, excision of extensive acute infarction (septum, anterior wall and apex) is not likely to be successful. It is, however, in precisely such patients that the removal of a segment exhibiting true paradoxical movement would be of the most significant benefit.

The probable optimal treatment for acute aneurysm at present is maximal rest, with impedance

reduction and early intraaortic balloon counterpulsation to maintain diastolic perfusion and promote development of collateral vessels. After between six and ten weeks arteriography should be done to identify other coronary lesions. If no serious additional coronary disease is present, then a prolonged program of impedance reduction and slow physical rehabilitation should be carried out. Extensive coronary vascular disease should be treated by revascularization, particularly when angina pectoris or other evidence of ischemia can be readily elicited.

Chronic established aneurysm presents a difficult set of therapeutic decisions. The presence of an established scar is associated in itself with minimal mechanical burden. Its excision may be associated with malfunction of the mitral valve apparatus, secondary to alteration of the geometry of the papillary muscles and chordae tendinae postoperatively. Nevertheless, a distinct benefit has been reported by several surgical groups[23,24] who did studies in patients in whom aneurysmectomy had been done alone and without myocardial revascularization; many such patients probably did not have additional extensive coronary disease. We have also noted spectacular improvement in certain patients. Whether this is due to revascularization, to more stringent adherence to the details of management by medical means, or to the excision of the scar itself probably varies from patient to patient, and a general statement is not applicable.

Because a fibrous aneurysm is unlikely to be the primary source of ischemic pain, its removal should be predicated on the relief of heart failure and improved cardiac function. Evidence on the latter issue seems variable. Our "early" studies, as in the reports of Fisher and co-workers,[10] Hazan and associates,[23] and Lefemine and colleagues,[24] show favorable directional changes, although of limited magnitude. The left ventricular end-diastolic pressure was reduced from 21 to 16 (our series), and reported from 35 to 25,[23] and from 19 to 17;[24] the ejection fraction improved from 0.29 to 0.36 (our series) and 0.27 to 0.40,[24] respectively. Favorable changes were reported in 69 percent of the patients studied by Loop and co-workers[3] but were not specified.

Review of the recent literature shows that the best outcome in terms of operative risk and long-term survival is found in patients without serious disease in coronary arteries other than that supplying the area of aneurysm. Of our patients, 94 percent had additional disease; other studies report 72 percent,[9,10] 74 percent,[2] and 100 percent (of 16 cases).[23] In this regard, of patients with symptoms of heart disease treated by aneurysm excision,[3] better results were obtained in patients with a lesser degree of native disease. The recently published experience of Sbokos and colleagues[25] seems similar in that most of the patients (18 of 20) did not receive bypass grafts.

Although our operative (30 day) mortality is low (6.6 percent), the total attrition rate (one year, 24 percent; three years, 53 percent) is similar to our parallel experience in severe power failure of the heart after extensive myocardial infarction.[26] These results closely parallel those reported by Cooperman and associates[9] (30 days, 18 percent; one year, 36 percent; two years, 43 percent) and by Fisher and associates[10] (30 days, 19 percent; 3½ years, 50 percent), who appear to be selecting comparable cases.

Finally, a large ventricular aneurysm can be present for many years, from diagnosis to death,[4] and yet not cause overt heart failure. Is the additional coronary and associated myocardial disease and not the aneurysm per se the most serious problem? Since the review by Gorlin and coworkers[16] in 1966, the availability of relatively safe surgical resection has not yet provided definite answers for the many aspects of the management of ventricular aneurysm.

Serious indication for the excision of aneurysm in symptomatic patients must include more than its identified presence. The pragmatic logic of a Willie Sutton should prevail over that of a George Mallory: "Why do you rob banks, Willie?" "Because that is where the money is." "Why do you wish to climb Mt. Everest, Mr. Mallory?" "Because it is there."

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Anticipating Cardiogenic Shock After Acute Myocardial Infarction

DWELLING ON THE kind of patient in whom cardiogenic shock tends to develop following acute myocardial infarction, I think therein lies the biggest clue to anticipating, and if possible avoiding—cardiogenic shock. Once it develops, little can be done because of the massive necrosis that accompanies it. But if one can anticipate what kind of clinical profile is likely to lead to cardiogenic shock perhaps we are in the best position to avoid the problem in the first place. The patient is generally 65 years old or older, and often has a previous history of myocardial infarction. An infarct a number of years ago that resulted in destruction of 20 percent of the left ventricle, when accompanied by a recent infarct that destroys another 20 percent, produces enough damage to the left ventricle to severely compromise its pumping action. So a previous myocardial infarction leads one to be concerned about subsequent development of cardiogenic shock. If the patient is hypertensive, he's more likely to have more damage because the increased left ventricular wall tension demands more oxygen; and the supply is inadequate and the demand not being met results in more extensive damage to the left ventricle. Diabetic patients tend to have cardiogenic shock because these patients often have widely distributed coronary disease which compromises large amounts of left ventricle. And, statistically, anterior myocardial infarctions tend to compromise ventricular performance to a greater extent than posterior myocardial infarctions. So that's the clinical profile of a patient who is likely to develop cardiogenic shock, even when you observe him within the first four hours following myocardial infarction and he seems to be reasonably comfortable.

—LESLIE WIENER, MD, *Philadelphia*

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Refer to: The kidney in multiple myeloma—Medical Staff Conference, University of California, San Francisco. West J Med 129:41-48, Jul 1978

The Kidney in Multiple Myeloma

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and Robert C. Siegel, Associate Professor of Medicine and Orthopaedic Surgery, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *At medical Grand Rounds this morning we will focus on the renal complications of multiple myeloma. Dr. Jane Melnick will present the case.*

Case Summary

DR. MELNICK:† The patient is a 90-year-old white man transferred from another hospital for evaluation of obtundation, anuria, fever and anemia. The patient had been in his usual state of excellent health until three weeks before admission. While vacationing in Hawaii, he sustained a spontaneous fracture of the left humerus. This was accompanied by fatigue and malaise. One week before admission, with an increase in his constitutional symptoms, he entered the first hospital; he was at that time ambulatory and oriented. Laboratory studies showed a hematocrit reading of 28 percent, a blood urea nitrogen (BUN) value of 38 mg per dl and a calcium value of 10.6 mg per dl. A barium enema study showed diverticulosis. An intravenous pyelogram which was undertaken to rule out obstruction showed decreased dye excretion, but a normal caliceal system insofar as it was visualized. Subsequent to the intravenous pyelogram, urine output was noted to fall to less than 10 ml per hour and this was accompanied by fever and a gradual deterioration in mental status until the day before transfer when the patient became unresponsive. A x-ray film of the chest was said to show a right lower lobe infiltrate; urine culture showed 10^5 Escherichia coli. Therapy was begun with intravenous administration of ampicillin and the patient was transferred to the University of California Medical Center 24 hours later.

Vital signs on admission showed a blood pressure of 120/76 mm of mercury, an irregular pulse of 80 beats per minute and a rectal temperature of 37.9°C (100.2°F). The patient responded only to deep pain. The pupils were equally round and reactive to light. The fundi showed no evidence of papilledema. The neck was rigid with pronounced meningismus, and there was no jugular venous distention to 10 cm at 30 degrees. On examination of the chest diffuse coarse rales and

*Lloyd H. Smith, Jr., MD, Professor and Chairman, Department of Medicine.

†Jane Melnick, MD, first year medical resident.

rhonchi were noted. First and second heart sounds were normal, but there were a soft apical third heart sound, a grade III/VI systolic ejection murmur at the lower left sternal border and a grade II/VI diastolic decrescendo murmur in the same distribution. The abdomen was distended with no bowel sounds heard; there were no masses. There was prostatic enlargement and a stool specimen was guaiac-positive. Extremities showed 1+ pitting edema. Results of neurological examination were significant for the presence of frontal lobe release signs and oculocephalic reflexes were normal. Corneal and gag reflexes were present. The four extremities moved symmetrically in response to pain, and there was diffuse increase in tone. The deep tendon reflexes were within normal limits. An electrocardiogram showed right bundle branch block with multiple premature atrial contractions. Pulmonary edema was noted on an x-ray film of the chest. A kidney, ureter and bladder study showed a paucity of bowel gas with a nasogastric tube in place, and a prolonged nephrogram phase. An x-ray of the left arm showed an extensive lytic process with an oblique fracture involving the humerus. Laboratory studies gave the following values: hematocrit, 31.6 percent; leukocyte count, normal; sedimentation rate, 140 mm per hour; peripheral blood smear showed rouleaux formation; sodium, 120 mEq per liter; potassium, 5 mEq per liter; bicarbonate, 16 mEq per liter; pH, 7.22; anion gap, 10; calcium, 8.3 mg per dl; phosphate, 7.5 mg per dl; uric acid slightly elevated at 8.6 mg per dl; serum viscosity, 2.2. Analysis of urine showed 2+ proteinuria by dipstick and 4+ proteinuria by 20 percent sulfa salicylic acid. The urine sodium value was 18 mEq per liter. A lumbar puncture and computerized tomography brain scan were entirely within normal limits.

The patient was admitted to the intensive care unit where cultures were obtained and broad-spectrum antibiotics were given. Urine output remained at 10 to 20 ml per hour despite the use of high dose furosemide, and the following day a Scribner shunt was placed in the right forearm. The first of many episodes of hemodialysis was carried out. BUN and creatinine values decreased accordingly. There followed a deterioration in ventilatory status with carbon dioxide retention requiring intubation and mechanical ventilation for 48 hours. The initial diagnosis of multiple myeloma was corroborated by a number of studies, including serum protein electrophoresis which showed 2.6 grams per dl of gamma globulin with a monoclonal spike. Immunoelectrophoresis showed an IgG kappa paraprotein with greater than 2,700 mg per dl IgG and a concomitant suppression of IgM and IgA. Urine protein electrophoresis showed 78 percent gamma globulin fraction, and urine light chains were greater than 1,200 μg per ml. Bone marrow aspirate showed 40 percent to 50 percent plasma cells, some of which were multinucleate. Long bone films showed myeloma involving the right, as well as left humerus, left scapula and clavicle, and findings on skull films were within normal limits.

The patient's pulmonary edema subsequently resolved rapidly with dialysis, mental status cleared gradually over a period of about one week, and he became entirely oriented and alert. Fever abated within 24 hours and administration of antibiotics was discontinued four days after admission when cultures were negative. With continued dialysis over two weeks, the BUN value fell to 35 mg per dl and the creatinine level fell to 2.5 mg per dl; they remained stable at these levels for at least ten days before discharge without dialysis. Spontaneous urine output simultaneously increased to one liter per day. One week after discharge the creatinine value had fallen to 2.1 mg per dl. The patient's multiple myeloma was treated with a four-day course of melphalan and prednisone, which was followed within ten days by a moderate pancytopenia. Outpatient follow-up examinations have since been done by the Medical, Orthopedic and Hematology-Oncology Services and subsequent courses of chemotherapy will be given.

DR. JAMES NAUGHTON:* Renal disease is the second most common cause of death in patients with multiple myeloma.[1,2] As illustrated by today's case, the course at times can be catastrophic and requires the most aggressive supportive care to insure patient survival. Other manifestations of myeloma may be subtle in their effects on the serum electrolytes and on urine protein excretion, and yet may provide very important diagnostic clues. Today, I wish to discuss four syndromes related to abnormalities of renal function in patients with multiple myeloma: (1) serum electrolyte abnormalities, (2) tubular abnormalities, (3) acute renal failure and (4) chronic renal failure.

The first of these syndromes deals with abnormalities of serum chemistry. There have been

*Assistant Professor of Medicine.

many references to the effect of myeloma proteins on the anion gap.[3,4] I prefer to calculate the anion gap simply by adding the serum chloride and bicarbonate values, and subtracting the sum from the serum sodium level. In order to simplify the arithmetic I do not use the serum potassium value in the calculations. The normal value for the anion gap is on the order of 12 mEq per liter with a standard error of about 0.5 mEq per liter.[3] These unmeasured anions are accounted for by the serum proteins, chiefly albumin, which are negatively charged; that is, they are anionic at physiologic pH. Albumin makes up about 75 percent of the normal anion gap. Immunoglobulins, particularly IgG, differ from albumin in that they are positively charged at the physiologic pH of serum. Therefore, if immunoglobulins accumulate in the blood, there will be a reduction in the calculated anion gap. Concomitant decrease in the serum albumin would further accentuate this decrease. In a review of this subject by Murray, the average anion gap in 50 patients with multiple myeloma was 9.2 mEq per liter, compared with 12.2 mEq per liter in controls.[3] This is statistically significant, although not so helpful clinically. However, almost a third of the patients with myeloma in that report had anion gaps less than 6 mEq per liter. This is several standard deviations away from the normal. Only two or three clinical entities can cause this: multiple myeloma, bromide poisoning—which has a completely different clinical presentation than myeloma—and some cases of severe hypernatremia which, of course, are already eliminated by initial measurement of the serum electrolytes.

The case presented today provides an interesting twist on the above observation. On admission the patient had a serum sodium level of 120 mEq per liter, a bicarbonate value of 16 mEq per liter and a serum chloride value of 94 mEq per liter. These yield an anion gap of 10 mEq per liter, very close to the normal range. However, the patient was in acute renal failure; the creatinine level was 7.8 mg per dl and metabolic acidosis was present with a pH of 7.22. This clinical situation should have resulted in an elevated anion gap, so the first diagnostic clue as to the underlying disorder could be obtained from the electrolyte determinations done on admission. When the acute renal failure with metabolic acidosis resolves there should be a reduced anion gap. This is exactly what happened. At the time of discharge the patient's anion gap was 5 to 6 mEq per liter. Before leaving the anion gap I want to point out that the same physiochemical properties of immunoglobulins that give rise to the narrowing of the anion gap also account for their failure to react with the urine indicator dye reactions for protein (dipstick). That reaction requires the presence of an anionic protein such as albumin. This will buffer hydrogen ions and cause a specific chemical reaction to produce the colorimetric change that identifies the presence of protein in the urine. Cationic proteins, including light chains, do not buffer hydrogen ion and therefore do not react.

The patient presented today provides a splendid example of the diagnostic information obtained by comparing the urine dipstick reaction and the sulfa salicylic acid reaction. The urine dipstick reaction was only weakly positive, whereas the sulfa salicylic acid reaction, which nonspecifically precipitates any protein, was grossly positive, suggesting the presence of cationic protein (immunoglobulin) in the urine. These two pieces of information, the inappropriately narrow anion gap and differential reaction for urine protein, strongly suggest the diagnosis of multiple myeloma.

Occasionally in patients with myeloma there will be a reduced serum sodium concentration; this factitious hyponatremia may even contribute to the reduction in the anion gap. There are two mechanisms by which this may occur. The first is simply the displacement of salt and water from any given aliquot of the serum by a large amount of paraprotein in the serum. This is entirely analogous to the hyponatremia seen with certain hyperlipoproteinemias. The other, and less common, difficulty with the measurement of the serum sodium occurs when there is co-existent hyperviscosity. This most frequently occurs in Waldenstrom macroglobulinemia, or with IgA myeloma wherein immunoglobulin molecules may polymerize. It rarely occurs in IgG myeloma. This is purely a technical problem related to the instrument used in the laboratory to measure the serum sodium level which uses an automated aspirating pump.[4] When the viscosity of the serum is elevated, the pump fails to aspirate the appropriate amount of serum, so it measures a smaller amount of sodium. Since the chloride is not measured by that same automated pump, its measured value may be normal. This will also result in an apparent lowering of the anion gap as well as hyponatremia, and can be corrected by having the laboratory manually pipette the serum sodium sample

TABLE 1.—*Renal Tubular Abnormalities in Myeloma*

Bence-Jones proteinuria
Light chains, molecular weight 20,000 daltons, filtered at glomerulus, normally reabsorbed *and* catabolized by renal tubules.
Appearance in urine may signify *either* overproduction and saturation of reabsorptive mechanism (myeloma) *or* renal tubular disease ("tubular proteinuria" systemic lupus erythematosus).
Light chains dimerize in acid pH to form Bence-Jones protein (molecular weight 40,000 daltons).
Proximal tubule dysfunction—Fanconi syndrome (glycosuria, phosphaturia, uricosuria, aminoaciduria).
Rare—about 15 cases, antedates clinical onset of myeloma.
Distal tubule dysfunction
Nephrogenic diabetes insipidus—in absence of hypercalcemia; only occurs in presence of Bence-Jones proteinuria.
Distal (gradient limited) renal tubular acidosis—only apparent with acid loading; correlates with presence of Bence-Jones protein.

in the presence of hyperviscosity. In the case discussed today, blood viscosity was determined; it was only minimally elevated and therefore was not contributing to the patient's low anion gap. The hyponatremia was not factitious and was a consequence of the patient's acute renal failure.

Hypercalcemia due to increased bone breakdown occurs during the course of myeloma in 50 percent to 60 percent of patients.[1] It may have profound consequences on renal function as well as on central nervous system function. Hyperuricemia also occurs, particularly after the initiation of treatment. This must be kept in mind and managed prophylactically to avoid the renal sequelae.

I shall turn now to consider some of the tubular abnormalities that may occur in myeloma (Table 1). In 1847 Henry Bence-Jones published a paper entitled "A new substance appearing in the urine of a patient with mollities ossium."[5] It may interest you to know that mollities ossium is not an antiquated term for multiple myeloma; it is an antiquated term for osteomalacia. Bence-Jones was not the first to observe this "new substance in the urine" but simply confirmed the observations of two others and published it first.[6] We know now that the proteinaceous precipitate that he observed when he warmed the urine of his patient to about 55°C, only to see it disappear with further heating, represents a dimer of light chains, either kappa or lambda, often found in patients with paraprotein disorders. Light chains are normally produced some 40 percent in excess of heavy chains. Light chains have a molecular weight on the order of 20,000 daltons and as such they are relatively well filtered at the glomerulus. Waldmann and his colleagues have shown that filtered light chains are reabsorbed and catabolized by the renal tubules.[7] Their appearance in the urine reflects either overproduction to the extent that the reabsorptive capacity is overwhelmed or a defect in tubular function.

We commonly make use of this information in two ways: the overproduction states such as multiple myeloma are associated with light chain (Bence-Jones) proteinuria; impaired tubular reabsorption may occur in patients with renal diseases such as lupus nephritis. Serial determinations of urinary light chain excretion may be useful in following the course of patients with lupus nephritis.[8] In the presence of an acid pH, light chains will form dimers which are less soluble. These dimers with molecular weights on the order of 40,000 daltons are what we recognize as the Bence-Jones protein. The less soluble dimerized form may precipitate in the tubules and cause tubular obstruction. This is the primary pathogenesis of chronic renal failure in myeloma, that is, myeloma kidney. It is uncertain whether excessive concentrations of light chains are directly toxic to tubular function independent of their mechanical obstructive properties. Preuss and his associates have shown that proteins extracted from the urine of patients with multiple myeloma are directly inhibitory to tubular transport functions in isolated rat kidney slices, whereas proteins extracted from the urine of patients with nephrotic syndrome are not inhibitory.[9] This would support the idea that light chains may be directly toxic to tubular function.[10] On the other hand, any disease process damaging renal tubules could be associated with an increase in light chain excretion. At present, this question is unresolved.

Several clinical conditions have been identified in which increased light chain excretion has been associated with tubular dysfunction.

Proximal tubular dysfunction has now been documented in some 15 patients with multiple myeloma presenting as a full-blown, adult-acquired form of the Fanconi syndrome.[11] In several of these cases, renal biopsy studies have shown the presence of large crystalline, electron dense deposits in proximal tubular cells, corresponding to similar crystalline dense deposits in the plasma cells of these patients. This is a rare finding and in only a handful of the 15 reported cases

TABLE 2.—*Acute Renal Failure in Multiple Myeloma*

Frequency: Approximately 7.5 percent (may be presenting manifestation of myeloma)
Causes:
Urography—rare (1 percent)
Hypercalcemia
Dehydration
Antibiotics
Sepsis
Prognosis: recovery frequent

have the appropriate histologic studies been done. It has been suggested that these deposits represent crystals of light chains, which accumulate in proximal tubule cells as a consequence of increased plasma cell production and reabsorption following glomerular filtration. They may be responsible for the multiple tubular transport defects seen in these patients.[11] Interestingly, these patients with the Fanconi syndrome did not have clinically obvious myeloma when they first presented. They had a pronounced increase in light chain excretion, symptoms of the Fanconi syndrome—generally weakness associated with hypophosphatemia—and all of the other associated tubular transport defects. Over a period of years, overt myeloma developed. This could be due to structurally different paraproteins that cause tubular toxicity when the overall tumor mass is much lower than in the usual case of overt myeloma.

Distal tubular dysfunction has also been reported in patients with myeloma and Bence-Jones proteinuria.[12] Nephrogenic diabetes insipidus in the absence of hypercalcemia may occur in the presence of Bence-Jones proteinuria and distal renal tubular acidosis has also been shown to be present in patients with myeloma.[12] Both of these defects have generally not been clinically obvious; that is, the patients were not polyuric, the concentrating defect was only shown when water intake was restricted and they were not clinically acidotic. Their urine acidification defect was only manifest when they were challenged with an acid load. Whether these last two defects which are clinically silent are the result of increased light chain excretion or simply an association remains to be determined.

We now move to the syndrome of acute renal failure (Table 2). The frequency of acute renal failure during the course of myeloma is unknown. The only large series in the literature is by DeFronzo and his associates. They reported 14 cases of acute renal failure which developed during the course of 187 cases of myeloma, a frequency of 7.5 percent.[13] As in the case discussed today, several patients have presented at the University of California, San Francisco, with acute renal failure as the initial manifestation of myeloma. Intravenous pyelography as a precipitating cause of acute renal failure in myeloma has been widely discussed since the original report by Bartel in 1954.[14] Several large retrospective reviews of patients with myeloma in whom pyelography has been carried out, indicate that the incidence of acute renal failure is approximately 1 percent.[15,16] Among the mechanisms suggested as the cause of acute renal failure are dehydration as a result of the bowel cathartics given before the radiographic procedure, osmotic diuresis from the contrast agent leading to dehydration and cast precipitation, urate deposition in tubules secondary to the uricosuric effect of radiographic dyes[17] and direct dye-induced protein precipitation. The radiographic dyes in use do not precipitate Bence-Jones proteins *in vitro*. However, angiographic dye may cause the precipitation of the so-called Tamm-Horsfall proteins, the tubular secretory proteins.[18] These proteins may begin to precipitate and cause tubular stasis and lead to precipitation of Bence-Jones protein with resultant tubular occlusion. Finally, direct vascular effects of the dye may cause vasospasm in the kidney, a low flow state, hyperconcentration of the protein within the filtrate and precipitation.[19]

On renal biopsy, these patients often are found to have extensive cast deposition within the renal tubules, unlike the acute tubular necrosis reported with angiographic procedures in other clinical situations. This suggests that the dye must play a role in the precipitation of Bence-Jones protein.

Other factors must be kept in mind, however, and may be more important than the role of pyelography in the development of acute renal failure in myeloma. In the review by DeFronzo only one of 14 cases of acute renal failure was associated with pyelography, whereas factors such as hypercalcemia, antibiotic toxicity and sepsis were more common.[13] Hypercalcemia has two effects: it can be directly nephrotoxic—through the mechanism of producing nephrocalcinosis—or it may induce the state of nephrogenic diabetes insipidus, a concentrating defect which predisposes the patient to dehydration and protein precipitation in the tubules. If acute renal failure develops in this setting, what is the prognosis? Most of the reports in the literature are not encouraging. In DeFron-

TABLE 3.—*Causes of Chronic Renal Failure in Myeloma*

"Myeloma kidney": tubular obstruction secondary to precipitations of Bence-Jones proteins, by far the most common lesion
Hypercalcemia—40 percent to 60 percent
Hyperuricemia
Amyloidosis—10 percent
Plasma cell invasion of kidneys—rare
Pyelonephritis

zo's series, nine of 14 patients died during the period of acute renal failure, and four of the remaining five died within two months.[13] However, that was a retrospective study garnered over a decade (from 1963 to 1973) which included a period where the aggressive dialytic support of patients with an underlying malignancy was less common.

At the University of California, San Francisco, we have seen three patients in the last two months with acute renal failure and multiple myeloma. In each instance, acute renal failure was the presenting manifestation of the disease. The only patient in whom an intravenous pyelogram was done was in the case presented today. Each of those three patients has recovered renal function after a period of hemodialysis and is now off dialysis and functioning out of hospital. Recent experience at the Mayo Clinic also supports a favorable outcome.[1]

Table 3 provides a differential diagnosis of the appearance of azotemia in a patient with myeloma. The most common cause is the first one—so-called "myeloma kidney," with a characteristic biopsy finding of tubulointerstitial disease with large, eosinophilic "hard" casts. These casts may appear laminated or fractured. They often provoke a proliferative response in the tubular epithelial cells with giant cell and syncytial formation. These casts are reportedly the longest seen in any renal disease and may occupy the full length of the nephron from proximal tubule to collecting duct. They predominantly contain Bence-Jones protein with some intact immunoglobulin, fibrinogen and Tamm-Horsfall protein.[20] The pathogenesis of myeloma kidney involves the filtration of light chains, dimerization of the light chains in the acidic urine leading to frank precipitation and trapping of various proteinacious elements within the tubules. There may be additional interstitial reaction and scarring and some secondary glomerular ischemia. Dehydration would accelerate this process by causing higher concentrations of protein in the filtrate. There are two experimental models to support this. In one model Bence-Jones proteins are parenterally injected into mice.[21] The other model involves innoculating mice with plasma cell tumors that secrete light chains. In this latter model, Bryan and McIntire have shown good correlation between tumor mass, the number of tubules containing casts and renal function.[22] Dehydrating these animals causes increased cast formation; maintaining a sustained diuresis with furosemide decreases cast formation. These results lend credence to our clinical impression that the state of hydration is indeed an important variable in the development of myeloma kidney.[22]

Hypercalcemia leads the other treatable causes of renal failure in myeloma (Table 3). An elevated serum calcium level occurs in 40 percent to 60 percent of myeloma cases at some point in the illness. Some degree of nephrocalcinosis is frequently present in biopsy specimens. Treatment of hypercalcemia in myeloma should first begin with a saline diuresis if tolerated, followed by prednisone. This is one of the hypercalcemic disorders that is quite responsive to prednisone therapy. Mithramycin is also effective in the more severe cases. Hyperuricemia, occurring primarily after the introduction of chemotherapy, can be prevented by prophylactic treatment with allopurinol and maintaining hydration. The dose of allopurinol should be reduced in those patients with significant renal insufficiency. Amyloidosis can be detected in about 10 percent of renal autopsy specimens in patients dying with multiple myeloma.[20] The protein deposited in primary amyloidosis consists of light chains. Primary amyloidosis is now considered part of the spectrum of plasma cell dyscrasias,[23] In myeloma, amyloid accumulation rarely impairs renal function. Clinically, the development of the nephrotic syndrome in a patient with myeloma suggests significant amyloidosis.[2] It carries no particular therapeutic implication as the treatment of the underlying disorder remains the same. Direct plasma cell invasion of the kidney has also been described. This appears even less common than amyloidosis and is almost never detected antemortem.[20] In a few cases massive retroperitoneal infiltration with plasma cells occurred and obstructive uropathy resulted.

Infection is the leading cause of death in cases of myeloma.[1] The urinary tract is a frequent site of infection and great care should be taken to avoid instrumentation in these high risk patients.

TABLE 4.—*Treatment of Renal Failure in Multiple Myeloma*

General principles: avoid dehydration, urinary tract instrumentation.
Treat hypercalcemia, hyperuricemia (expectantly)
Cautious use of nephrotoxic antibiotics
Intravenous pyelography if indicated
Specific treatment: forced diuresis and alkali therapy have been suggested, no controlled data.
Dialysis: both acute and chronic.
Four of seven patients in recent series survived longer than one year
Renal transplantation: may be considered in stable patients who have achieved remission with chemotherapy

While a urinary tract infection should always be considered a likely source of sepsis in these patients, it is a rare cause of renal failure.

I would like to briefly comment on renal insufficiency in Waldenstrom macroglobulinemia. It differs from multiple myeloma in that the predominant renal lesion is glomerular, not tubular. It consists of the accumulation of large hyaline thrombi on the capillary lumen.[24] Immunofluorescence staining shows these deposits to be primarily composed of IgM. Tubular casts are uncommon and not nearly so widespread in Waldenstrom macroglobulinemia as they are in myeloma. Treatment is directed at the primary disorder.

In all of these disorders, then, histologic examination of the kidney is not likely to change the treatment. Except in most atypical situations, a renal biopsy study need not be done in patients with multiple myeloma.

In considering treatment (Table 4), a few general principles are important: avoid dehydration which may lead to excessive cast formation and avoid urinary tract instrumentation in these infection-prone patients. Hypercalcemia and hyperuricemia are among the most treatable sequelae of myeloma and they should be aggressively pursued. Nephrotoxic antibiotics have been implicated in a significant number of patients in whom renal failure develops with myoloma. It has been suggested that in the presence of Bence-Jones proteinuria, antibiotic toxicity may be enhanced.[13] There is no direct evidence to support this, but nephrotoxic antibiotics should be administered at reduced doses in those patients who have renal insufficiency. Serum levels should be monitored. Pyelography does not pose an undue risk to patients with myeloma in whom hydration is adequate. However, if the diagnosis of myeloma is made, there is really no indication for an intravenous pyelogram in a vast majority of cases. The presence of the paraprotein disorder is a sufficient explanation for renal insufficiency. If obstructive symptoms also are present, or there are physical findings suggestive of urinary tract obstruction, then a pyelogram carried out with adequate hydration is a reasonable diagnostic procedure. Under these conditions, the incidence of acute renal failure may be kept to 1 percent.

There is evidence from both animal studies and several anecdotal clinical reports that forced diuresis and alkalization of the urine will prevent or ameliorate myeloma kidney.[21,22,25] There are no controlled clinical data. In patients who can tolerate sodium loading, the ingestion of 3 to 4 liters of fluid per day and about 10 grams of sodium bicarbonate has been recommended as possibly beneficial in the face of developing renal insufficiency and documented Bence-Jones proteinuria.[25]

There is growing experience with both acute and chronic hemodialysis in patients with multiple myeloma. We would consider patients in whom acute renal failure develops to be suitable for dialysis if they are otherwise candidates for continuing treatment of their myeloma. Our recent experience suggests that they have a reasonable chance to recover renal function and not require long-term dialysis. There are also several reports of patients with myeloma doing well on programs of long-term dialysis. In a recent series by Vaziri and his colleagues, four of seven patients receiving long-term dialysis survived for at least a year, and two of seven were alive after three years.[26] It appears that patients with myeloma whose only major disability is renal failure and in whom additional chemotherapy is planned can be considered for long-term hemodialysis. Their tolerance for chemotherapy appears to be significantly improved when a program of long-term dialysis is being carried out.

There have been a very few case reports of renal transplantation in patients with myeloma and chronic renal failure.[27] In these patients hemodialysis had been maintained and remission of myeloma was achieved with chemotherapy. This is a most unusual combination of events. One such patient has received a renal transplant at this medical center. The diagnosis of multiple myeloma was established two years before transplantation, renal failure developed as a result of the myeloma, the patient was maintained on he-

modialysis and there was a complete hematologic remission on chemotherapy. A kidney was transplanted from a cadaver and the patient is doing well a year and a half after the transplant without recurrence of the myeloma. The age of patients with myeloma places many of them beyond the 60-year age limit for transplant candidates accepted by our Kidney Transplant Service.

In the case discussed today there were abnormalities in each of the four areas I have outlined. The patient had a reduced anion gap, he was hypercalcemic and hyperuricemic. He had Bence-Jones proteinuria, and acute renal failure developed superimposed on chronic renal failure. The excellent care provided by the house staff shows that in spite of his advanced age and underlying malignant condition it is possible to restore a satisfactory quality of life to someone this severely afflicted.

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Important Advances in Clinical Medicine

Epitomes of Progress—Internal Medicine

The Scientific Board of the California Medical Association presents the following inventory of items of progress in internal medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in internal medicine which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Internal Medicine of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Characteristics of Gonococci Which Disseminate in the Blood

GONOCOCCI infecting the genitalia, pharynx or rectum may invade the blood to produce a variety of syndromes collectively called disseminated gonococcal infection (DGI). The most common syndrome of DGI, arthritis-dermatitis, results from the initial bacteremia and is characterized by fever and chills, typical skin lesions, and arthralgias or transient arthritis of the knees, wrists, hands or ankles. Infection of a large weight-bearing joint secondary to bacteremia (septic joint) may present as a typical, culture-positive, purulent arthritis with minimal systemic symptoms and negative blood cultures. Metastatic infection of the heart (endocarditis or pericarditis) or the meninges may present with findings typical of these diseases.

Three recently described characteristics of DGI isolates help to explain important features of the disease:

1. They are slow-growing and nutritionally fastidious requiring several growth factors not needed by most local isolates. This may explain the high incidence of asymptomatic local infections and the diffculty in growing them from the blood.

2. Despite increasing resistance to penicillins among other strains, DGI isolates remain extremely sensitive. For this reason, relatively short, low-dose penicillin regimens (for example, 3.5 grams of ampicillin given orally plus 1 gram of probenecid followed by ampicillin 500 mg every six hours for seven days) are effective for the arthritis-dermatitis syndrome.

3. Finally, two observations suggest that complement-mediated lysis of gonococci protects against DGI. First, DGI isolates uniformly resist lysis by antibody and complement in normal human serum, whereas only about two thirds of local isolates are serum-resistant. Therefore, only those local strains that resist killing by serum can invade the blood. Second, rare patients, deficient in one of the terminal components of complement responsible for bacterial lysis (C_6 to C_9), suffer recurrent gonococcal or meningococcal bacteremias. Because in these patients opsonization of gonococci occurs normally through the early components of complement (C_3 and C_5) but does not kill them, these cases illustrate an important role of serum killing in preventing DGI.

The tendency for DGI to be associated with asymptomatic local infections and to respond to

low doses of penicillin, therefore, can be attributed to unusual characteristics of invasive gonococci. Recurrent neisserial bacteremia should alert physicians to a genetic deficiency in terminal complement components. Immunization to improve killing of resistant gonococci in the blood is a promising approach to prevention of DGI.

J. ALLEN McCUTCHAN, MD

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Clinically Applicable Radioimmunoassays of Parathyroid Hormone

BOTH INTACT 84-amino-acid biologically active parathyroid hormone (PTH 1-84) and biologically inactive carboxyl-terminal ("C") fragments of PTH 1-84 circulate in human blood. The "C" fragments are derived both from the parathyroid glands and from the peripheral metabolism of PTH 1-84. Their concentration in the peripheral blood is relatively higher than PTH 1-84 because they survive longer in the circulation.

Serum radioimmunoassays (RIA) of PTH using antisera that react well with circulating "C" fragments ("C" assays) distinguish normal from hyperparathyroid subjects better than assays that detect only PTH 1-84. RIA's using antisera that react only with intact PTH 1-84 ("I" assays) are better in showing step-up differences between peripheral serum immunoreactive PTH (iPTH) and iPTH in serum draining parathyroid tumors.

All generally available RIA's of PTH have been developed with nonhuman reagents. Likewise, their ability to detect intact (amino terminal) or carboxyl terminal PTH have been determined with fragments of bovine PTH. Such studies do not adequately characterize the specificity of assays for *human* PTH. Fragments of human PTH are not commercially available.

At present, the only (and probably the best) way to characterize RIA's to be used for diagnostic purposes in humans is to determine the species of iPTH circulating in human peripheral serum recognized by a given RIA. This can be done easily by measuring the iPTH in the effluent fractions of gel-filtered hyperparathyroid serum and this information should be available to the user. Therefore, assuming adequate sensitivity, RIA's which recognize both intact PTH 1-84 and the larger molecular weight carboxyl terminal fragments of PTH in hyperparathyroid serum are "C" assays and can be expected to provide excellent discrimination between normal subjects and patients with hyperparathyroidism. RIA's which recognize primarily intact PTH can be expected to give the greatest step-up differences between peripheral and parathyroid venous effluent serum obtained during parathyroid localization procedures.

Selecting an appropriate RIA of PTH for diagnostic application has become a difficult and somewhat exasperating chore for most physicians because of the exponential growth in the number of assays available and competition-induced claims of advantages of one assay over another. The simple criteria given in this epitome for selecting clinically applicable RIA's for PTH should be helpful in making objective choices.

CLAUDE D. ARNAUD, MD

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Hepatotoxicity Caused by Acetaminophen or Salicylates

ACUTE ACETAMINOPHEN OVERDOSAGE may result in massive hepatic necrosis with encephalopathy and death. Toxicity is mediated by an oxidized metabolite of acetaminophen that depletes intracellular glutathione levels. Generally, single doses in excess of 15 grams are required, although severe liver damage has occurred with ingestion of 10 grams in the presence of alcohol or drugs that induce the microsomal enzymes. Therapeutic dosages consumed for several weeks may also cause hepatitis with elevation of the serum transamines, alkaline phosphatase and bilirubin; centrilobular necrosis may occur. As little as 3 grams a day may be hepatotoxic, although injury seems more common at levels of 5 to 8 grams per day. The inflammation and necrosis are reversible on cessation of the drug, and no cases of cirrhosis have been reported with either acute overdosage or chronic ingestion.

Unlike acetaminophen, acute salicylate intoxication does not result in hepatic necrosis. Chronic ingestion of salicylates, however, in patients with acute rheumatic fever, juvenile rheumatoid arthritis, systemic lupus erythematosus or Reiter syn-

drome may lead to elevation of hepatic enzymes. Toxicity is unusual at serum salicylate levels of less than 20 mg per dl, but in one series toxicity occurred in all patients with juvenile rheumatoid arthritis in whom levels were greater than 25 mg per dl. Liver biopsy studies show a mononuclear cell infiltrate of the portal triads with scattered cellular necrosis that occasionally is consistent with chronic active hepatitis. As with acetaminophen, the toxicity is reversible. Lower dosages can be reinstituted providing the hepatic enzymes and serum salicylate level are monitored closely.

GERRY BOSS, MD

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Cimetidine in the Treatment of Peptic Ulcer Disease

A NEW CLASS of compounds, termed the histamine type 2 or H-2 receptor antagonists, has been added to the ever-expanding list of drugs used in the treatment of acid peptic ulcer disease. Cimetidine, the only H-2 antagonist currently available in the United States, has undergone extensive basic research testing and clinical trials documenting its ability to profoundly decrease gastric acid secretion. Histamine receptors on the gastric parietal cell playing an important role in the stimulation of hydrochloric acid secretion through all modalities (cephalic phase by vagal innervation, stimulated by food and stimulated by gastrin) are not antagonized by the traditional antihistamines (called H-1 receptor antagonists) such as diphenhydramine (Benadryl®). The H-2 receptor antagonists, such as cimetidine, block to a major degree the acid output stimulated by all known gastric secretagogues.

Early H-2 receptor antagonists, particularly metiamide, were found in some clinical trials to be associated with neutropenia on rare occasions. However, no significant toxicity has been found with cimetidine use, although isolated reports of gynecomastia have appeared. Cimetidine cannot yet be recommended to pregnant or nursing women.

Cimetidine has been shown to be effective in healing duodenal ulcers. Gastric acid secretion and acid delivery to the duodenum are significantly reduced with cimetidine therapy and it is associated with an improved rate of ulcer healing. Studies are in progress assessing the efficacy of cimetidine therapy in gastritis and gastric ulceration, as well as the prophylactic usefulness of continuous long-term nocturnal cimetidine administration for acid peptic disease.

Cimetidine usage should be considered in patients with gastric acid hypersecretory states such as Zollinger-Ellison syndrome and systemic mastocytosis and in patients who cannot or will not take effective doses of antacids for duodenal ulcer disease. The oral dosage is one 300 mg tablet with each meal and an additional 300 mg at bedtime. A parenterally administered form is available for patients who cannot take orally given medication. The drug should be administered in these latter patients in a dosage of 300 mg (mixed with 100 ml of a 5 percent dextrose solution) every six hours. The drug should not be used for dyspepsia without documented duodenal ulceration and it should be used with caution in patients with routine duodenal ulcers. With this drug, as with all new drugs, practicing physicians must be alert to unusual, unreported manifestations of toxicity.

JOHN P. CELLO, MD

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Pituitary Cushing Syndrome: New Options for Treatment

HYPERCORTISOLISM in two thirds of all cases is secondary to excessive secretion of adrenocorticotropic hormone (ACTH) by the pituitary gland (pituitary Cushing syndrome). The mainstay of treatment for more than three decades has been total bilateral adrenalectomy. This treatment has brought its own problems including a significant mortality rate, persistent or recurrent hypercortisolism due to hyperplastic remnant or ectopic adrenal tissue, postoperative pituitary tumors (Nelson syndrome) and, almost invariably, lifelong dependence upon replacement therapy with adrenocortical hormones. Recent therapeutic advances now offer promise of making total adrenalectomy obsolete over the next few years.

Pituitary radiation has been used with limited success as a primary treatment in adults, perhaps

only 15 percent to 20 percent of cases being fully responsive to ^{60}cobalt radiotherapy in doses of 4,000 to 5,000 rads. However, children appear to be considerably more radiosensitive than adults and, as recently reported, as many as 80 percent can be effectively treated with radiation alone. While the lag period for full benefit may be as long as 18 months in some cases, the procedure is essentially free of morbidity, no hormone replacement is required and pituitary function has remained intact after prolonged follow-up. Based upon these encouraging results, cobalt radiotherapy can be expected to become the preferred initial treatment for pituitary Cushing syndrome in patients under 20 years of age.

Clinical trials of selected drugs have not as yet produced an agent which can be considered as sole definitive treatment. Mitotane, an adrenocorticolytic drug, has proved to be a useful adjunct for short-term improvement of patients who are incompletely treated or who are awaiting the full effects of radiation. An entirely novel, recent approach has been the introduction of two agents believed to alter brain neurotransmitter regulation of pituitary ACTH. Both cyproheptadine, a serotonin antagonist, and bromocryptine, a dopamine agonist, can ameliorate clinical features and reduce cortisol production. Careful studies of cyproheptadine indicate that not all patients are responsive and, when therapy is effective, relapse promptly follows discontinuation of the drug. However, the minimal side effects and possibility of spontaneous remissions with more prolonged treatment make these agents attractive for continuing clinical evaluation.

The single most impressive advance in management of pituitary Cushing syndrome has come with refinements in surgical procedures to the pituitary gland, now emerging as the treatment of choice in adults. This is due, in part, to improvements in radiologic diagnosis, particularly tomography, which has enabled the detection of pituitary microadenomas in more than 50 percent of patients, compared with the 5 percent in whom diagnosis is possible using conventional x-ray studies of the skull. These small tumors can now be viewed directly and resected, leaving the rest of the pituitary intact, using microdissection techniques made possible by the coupling of transsphenoidal surgical procedures with newer surgical microscopes. Two recent reports confirm 90 to 95 percent remission rates following removal of microadenomas and, equally impressive, this has been achieved without operative mortality and in almost all cases without permanent pituitary failure. It is noteworthy that whereas surgical operation in one series was used only in patients in whom abnormalities were shown on radiographs, Wilson and his group successfully operated on 16 of 17 patients despite normal findings on tomograms in 40 percent of them. This has led the latter group and others to advocate surgical exploration of the sella for every patient with pituitary Cushing syndrome regardless of tomographic findings. Another decade of experience may be required to clearly establish that removal of such microadenomas can be done safely with prolonged remission of Cushing syndrome and preservation of normal pituitary function. However, the short-term results make it apparent that at least for the next decade pituitary surgical therapy has replaced total adrenalectomy as the primary treatment for adults with pituitary Cushing syndrome.

ERNEST M. GOLD, MD

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Anaerobic Infections and Metronidazole

WITH NEWER MICROBIOLOGICAL TECHNIQUES, anaerobic infections are now recognized as a substantial hospital problem. These include particularly postsurgical, posttraumatic, female pelvic and pleuropulmonary infections; and anaerobes are a common component in abscess formation. In cases of sustained anaerobic bacteremia, mortality approaches 50 percent.

Currently available antibiotics against anaerobes have gaps in their spectrum of activity, most notably against Bacteroides species or major toxicity. Bacteroides species make up 10 percent of all bacteremias recognized in hospital.

Metronidazole has a broad spectrum of antimicrobial activity and its utility against amebic and trichomonal infections is well known. It also has rapid irreversible bactericidal action *in vitro* against anaerobes, including Bacteroides. In man, it penetrates well from the blood into body fluids

and appears to concentrate selectively in abscesses. It does not appear to antagonize other antibiotics.

It has been shown effective in treatment of patients with anaerobic sepsis or endocarditis, meningitis and brain abscess, posthysterectomy and postpartum pelvic infections, lung abscess or empyema, including patients who failed to respond to other antibiotics. In these cases, bactericidal blood concentrations correlate with successful outcome. It has also been effective in prophylaxis in bowel surgical procedures, appendectomy and gynecologic surgical operations.

Its use in antianaerobe therapy has been considered experimental in the United States in the absence of licensing for this indication. It has been available for oral administration only, but is absorbed after rectal administration and an intravenously given preparation is under study, which would allow therapy of seriously ill patients.

Side effects are minimal and infrequent, and include gastrointestinal disturbances at high doses, transient leukopenia and sensory neuropathy, headache and vestibular symptoms. Mutagenesis has been shown in bacteria but is of uncertain relevance, particularly because certain intracellular conditions correlated with this effect in bacteria have not been shown in humans. Carcinogenicity occurs in some rodents, but this is of uncertain significance since the doses and duration used in these experiments bear no relation to that used in human therapy.

Studies here and abroad indicate that this agent, at present undergoing further trials and possibly available in the future for general use in antianaerobe therapy in the United States, represents a major therapeutic advance—particularly against Bacteroides.

CORSTIAAN BRASS, MD
DAVID A. STEVENS, MD

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Hepatitis B Immune Globulin in the Prevention of Hepatitis B

HEPATITIS B is a common infection reaching epidemic proportions in some populations. Previously referred to as "serum hepatitis," hepatitis due to the B virus is now known to be transmitted not only by parenteral routes but also by close physical contact and exposure of mucus membranes to the virus. Hepatitis B is easily diagnosed by showing the presence in serum of hepatitis B surface antigen (HB_sAg) or by a rising titer of antibody against the surface antigen (anti-HB_s). Recently, a preparation of hepatitis B immune serum globulin (HBIG) has become available.

HBIG can cost more than $150 per injection and two doses, approximately 30 days apart, are recommended. For comparison, ordinary gamma globulin (immune serum globulin, ISG), which may contain appreciable titers of anti-HB_s, costs less than $10.

HBIG is prepared from plasma in a manner similar to common ISG except that the donor source of plasma is high in titer of anti-HB_s. Both preparations are safe, neither transmits hepatitis, and side effects from intramuscular administration are low. HBIG has been shown in several controlled trials to reduce the likelihood of clinical illness and seroconversion due to hepatitis B. One large study of needle puncture exposure reported a 1.4 percent incidence of clinical hepatitis and a 5.6 percent seroconversion (anti-HB_s) in subjects given HBIG. This was in contrast to a 5.9 percent incidence of clinical hepatitis and a 20.7 percent seroconversion of subjects receiving immune serum globulin containing uncommonly *low* levels of anti-HB_sAg.

The United States Public Health Service Advisory Committee on Immunization Practices recommends the use of HBIG for patients with a single exposure to blood containing hepatitis B virus. This contact can take several forms, including needle puncture, mucus membrane contact or open wound contamination. Other less well established indications for HBIG use include exposure to body fluids other than blood products (urine, saliva, stool and the like), close physical contact with carriers of HB_sAG, and constant environmental exposure such as occurs in hemodialysis units or custodial institutions for the mentally retarded.

The initial intramuscular dose of 0.05 to 0.07 ml per kg of body weight should be given as soon as possible after exposure (not more than 7 days) and is followed by a second injection 30 days later. Confirmation of the HB_sAg positivity of the donor is mandatory and showing the absence of anti-HB_s is desirable if testing will not unduly delay gamma globulin prophylaxis. Chronic contact such as occurs in spouses of chronic carriers is not a sufficient indication for HBIG administration. Detailed questioning of the circumstances surrounding the actual exposure is necessary since many

patients overemphasize the significance of their exposure because of anxiety. When doubt arises regarding the exposure, routine ISG therapy can be used as an alternative to HBIG because most currently available preparations of ISG contain significant levels of anti-HB_s and may prove to be as effective as the more costly preparation.

HOWARD P. SHERR, MD

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Medical Versus Surgical Treatment of Coronary Artery Disease

IT IS ESTIMATED that in 1977 myocardial revascularization operations were carried out in approximately 70,000 patients. Recent studies, however, have questioned the efficacy of coronary artery bypass procedures in prolonging life. The most noteworthy of these are the multicenter randomized study on unstable angina and the Veterans Administration cooperative study on chronic stable angina. The unstable angina study required the patients to have unstable or changing anginal symptoms in association with electrocardiographic changes during pain. These patients had to have at least a 70 percent stenosis of one or more of the major coronary artery branches. At the end of 24 months there was no statistically significant difference between the mortality of the surgical (5 percent) versus the medical (6 percent) group. It was remarkable that a third of the medically treated patients crossed over to the surgical group because of lack of adequate control of symptoms with medication. It was significant that there were three times as many medically treated patients in the functional class 3 to 4 group as surgically treated patients. The hospital mortality was not significantly different between medical (3 percent) and surgical (5 percent) groups. The myocardial infarction rate on the initial hospital admission was higher in the surgical group (17 percent) than in the medically treated group (7 percent) and this was statistically significant.

The Veterans Administration study on chronic stable angina showed no significant increase in the survival of medically treated patients versus surgically treated patients with one-, two- or three-vessel coronary artery disease. The major objections to this study are a graft closure rate of 31 percent and a surgical mortality of 5.6 percent, which are considerably higher than those published by many other institutions during the same period (1972 through 1974). This study did show, however, that patients with left main coronary artery disease fared significantly better with surgical than medical therapy.

At present at most major institutions the early hospital mortality for saphenous vein bypass surgical operation is 1 percent to 2.5 percent and the graft patency rate is 85 percent to 90 percent at 3 to 12 months. It is likely, though not yet proved, that in these centers longevity might be enhanced in the surgically treated groups. Though only improved longevity for patients with left main stem coronary disease has been confirmed, the quality of life for surgically treated patients seems to be better because 70 percent of them will be totally relieved of angina whereas only 30 percent of medically treated patients will be completely relieved. This could be especially important in young active patients who might survive a large myocardial infarction but be limited by angina or reduced ventricular function.

Physicians should be keenly aware of the surgical results of the centers to which they refer patients. The continuing national multicenter studies will shed more light on this controversy.

WILLIAM H. WILLIS, JR., MD

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Diagnosis of Sjögren Syndrome

SJÖGREN SYNDROME (SS) is the second most common (and perhaps least well-known) connective tissue disease. Its estimated prevalence may be as high as 1 in 200. Sjögren recognized the generalized nature of the disease and defined the characteristic triad of keratoconjunctivitis sicca (KCS), xerostomia and chronic arthritis. Studies from several centers over the last decade have indicated the systemic and autoimmune nature of the disease, and the possible relationship to malignant lymphoproliferation. The hallmark of the disease is lymphocytic infiltration which can involve lung, liver, kidneys and muscles. Rheumatoid factor, antinuclear factor and other autoantibodies occur frequently.

Labial salivary gland (LSG) biopsy study is a major advance in diagnosis, permitting histopatho-

logic confirmation of destructive lymphocytic infiltration. Multiple aggregations of lymphocytes replacing and destroying the acinar tissue characterize the lesion. An aggregate of more than 50 lymphoid cells is called a focus. More than one focus per 4 sq mm of glandular tissue is characteristic of SS, whereas such focus scores (greater than one) are found in less than 1 percent of either living or autopsy controls of all ages.

Although several techniques (such as measurement of salivary flow rate, scintiscan and sialography) can be used to document objective salivary gland dysfunction, only the presence of the characteristic histopathology is specific for SS. LSG biopsy is also more sensitive and specific than ocular examination for KCS in establishing the diagnosis of SS. The biopsy specimen should be obtained when a patient is not receiving high or rapidly changing doses of prednisone or other lympholytic agents because these may alter the findings.

Two of the following three criteria are necessary to definitely diagnose the connective tissue disease first elucidated by Sjögren:

- Characteristic lymphocytic infiltrates demonstrable on salivary gland biopsy studies,
- Definite KCS and
- An associated extraglandular connective tissue or lymphoproliferative disorder.

In our series, only 25 percent of patients have rheumatoid arthritis. Another 15 percent have systemic lupus erythematosus, scleroderma or polymyositis. In nearly half of cases there are typical extraglandular connective tissue and lymphoproliferative features in the absence of criteria for another coexisting connective tissue disease.

Because SS appears to represent an immunologic attack on exocrine organs, we have proposed the term autoimmune exocrinopathy (AE) to describe the syndrome better. AE is easily confirmable by an LSG biopsy study. Its presence may help diagnose unexplained systemic abnormalities suggestive of a connective tissue disorder.

Only 50 percent of patients referred for SS actually have an autoimmune disease. Other frequent causes of oral and ocular dryness include local glandular disorders, anxiety-depression syndromes and parasympatholytic drugs.

SS is the only connective tissue disease associated with transplantation antigens HLA-B8 and HLA-Dw3 and with the precipitating antibodies Ha, SS-A and SS-B which react with nuclear antigens. These are unique precipitins which can distinguish SS from other connective tissue diseases.

SS appears, therefore, to be a unique connective tissue disease related to but genetically, serologically and histopathologically distinguishable from rheumatoid arthritis, systemic lupus erythematosus or other connective tissue diseases. These latter disorders need not be present and therefore should not be required for diagnosis. The characteristic histopathology of the disease is most easily shown by results of LSG biopsy studies and may precede the exocrine gland dysfunction described by Sjögren.

RICHARD A. PITTSLEY, MD
NORMAN TALAL, MD

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Antinuclear Antibody Testing

ALTHOUGH ANTINUCLEAR ANTIBODY TESTING was discovered some years ago, it is only recently that this test has become widely available. Because both the techniques of carrying out the test and the methods of reporting it vary, accurate clinical application of this immunologic test can be somewhat difficult.

As with any laboratory test, there are a certain number of false positives. Two percent of young adults will be positive at low titers (usually speckled pattern trace to 1+ at 1:16) in the absence of clinical evidence of any disease process. The percentage of false positive antinuclear antibody (ANA) tests in normal subjects rises to approximately 6 to 8 percent in persons more than 60 years old. This may be due to gradual loss of immunologic control resulting in antibody formation against nuclear constituents of cells undergoing the natural breakdown process.

In an endeavor to avoid the trap of diagnosing systemic lupus erythematosus or other autoimmune disease simply on the basis of a positive ANA titer, several items can be reported: (1) the strength of positivity on a scale of 0 to 4+; (2) serial tube dilutions and (3) the staining pattern.

The strength is important since most of the above noted normal subjects presenting with a positive ANA titer will have a strength of only trace to 1+ in the lower tube dilutions (1:10,

1:20 or 1:16, depending on the laboratory method). These all become negative at the 1:40 or 1:64 range. Some laboratories report "ANA positive" or "ANA negative." If the specimen is tested only undiluted, the percentage of positives will be much higher even than the 2 to 8 percent noted above; therefore, it is essential to have results on a diluted specimen to avoid excess numbers of false positives.

The pattern of staining can also be useful. Four types of patterns are quite readily discernible especially when present in high concentration: rim or shaggy, homogeneous, speckled, and nucleolar. These patterns represent various groups of antibodies, some of which are known to have clinical significance. The rim pattern is often seen in active systemic lupus erythematosus, especially when there is kidney involvement. The homogeneous pattern, especially when strong and at high titer, often represents active systemic lupus erythematosus. The speckled pattern is more variable and it is here that the greatest numbers of false positives are found. When strong, this pattern can represent mixed connective tissue disease, in which case a test for antibodies to ribonucleoprotein (RNP) or Sm antigen can be done. If the RNP antibody titer is high and there are no Sm antibodies, mixed connective tissue disease can be diagnosed in the appropriate clinical setting. If RNP and Sm antibodies are present, systemic lupus is suspected. The speckled staining pattern will also often be positive in progressive systemic sclerosis. The rarest pattern is the nucleolar which can be present in progressive systemic sclerosis, Sjögren syndrome or rarely other autoimmune disease.

Testing for antinuclear antibodies has largely replaced the lupus erythematosus or LE cell test, because of its greater reliability and its greater range of antibody detection. Since the LE cell test only detects one antibody (deoxyribonucleoprotein), it is present in only 70 percent of cases of systemic lupus, whereas the ANA titer should be positive in nearly 100 percent of such patients. Since the LE cell test is somewhat more difficult to run accurately and to read, and since it requires repeating on two to three different specimens for even marginal reliability, it is being replaced by the ANA test.

When can clinicians appropriately order an ANA test? When the clinical suspicion for systemic lupus or other autoimmune disease is strong, ANA positivity helps in confirming the diagnosis. (However, without strong clinical suspicion on the basis of careful history and physical examination, a positive ANA titer should *not* be construed to indicate a diagnosis of systemic lupus erythematosus.) The second use of the ANA test is in following the course of the disease process by noting the change in strength of testing and tube dilution, which can help confirm disease remission or exacerbation.

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EDITORIALS

From Curing to Caring

MEDICAL SCIENCE has not always been at its best in the management of an incurable, suffering terminally ill patient. Too often to a medical scientist physician, the impending death of a patient seems to be viewed as an impending defeat both for the physician and for medical science itself—something to be prevented or delayed at any, literally any cost, whether to the patient, the family or to society. As an example, one can recall the death of General Douglas MacArthur, where every resource of medical science was thrown into the fray, and one cringes at the uselessness of it all not to mention the repeated indignities to that great and above all dignified national hero.

One now can begin to sense the start of what one hopes will be a growing trend toward a better balance of curing and caring in patient care. Curing, when it can be accomplished at a reasonable cost in dollars and a suitable reward in quality of life, is one thing and certainly is to be desired. But when this cannot be accomplished, as is all too often the case, more emphasis on caring is sometimes needed. This of course is what medicine is all about as the term medical care itself attests. The common usage is medical care and not medical cure. If there indeed is to be a growing trend toward or emphasis upon caring, it is interesting to speculate that economic factors of cost control may likely combine with a rejuvenation of humanism in medicine to bring this about.

This appears to be just what is happening in the development of the hospice movement which is discussed elsewhere in this issue. Both economic and humanistic factors are clearly at work. Even the very sparse data available seem to show that the process of dying with a terminal illness can be accomplished economically and with some comfort and considerable dignity in the circumstances and under the auspices of a hospice. It is therefore important for many reasons that this worthwhile and important movement be encouraged by the medical profession and the society it serves, and that it be kept within the mainstream of patient care. Consequently, it is most appropriate that criteria and procedures for the accreditation of hospices be developed and that this be accomplished as soon as possible. Caring has always been as important to mainstream medicine as curing—and it still is.

—MSMW

Ventricular Aneurysms

THE SPECIALTY CONFERENCE from the University of California, Los Angeles, by Swan and associates in this issue contains an excellent discussion of the clinical problem of ventricular aneurysms. This study summarizes the recent clinical experience at Cedars-Sinai Medical Center, Los Angeles, including ventriculographic data, coronary anatomy and surgical techniques. The importance of aneurysms in the distribution of the left anterior descending coronary artery is emphasized by the data. Since it has often been difficult to judge the effects of an acute myocardial infarction on subsequent ventricular function, this report nicely summarizes the important considerations which help in understanding the deleterious effects of a ventricular aneurysm.

One of the immediate problems in dealing with this subject is the definition of an aneurysm.[1] Since ischemic, infarcted and scarred areas may be akinetic, but not necessarily bulge paradoxically, the identification of aneurysms has often been difficult because the definition is not standard. In this regard, the article provides an analysis of left ventricular contours (from ventriculograms) which provide a reasonable format for characterizing left ventricular aneurysms.

More important, this article summarizes some of the pathophysiologic consequences of ischemia, infarction and subsequent fibrosis.[2] Of importance is the acute paradoxical expansion in early aneurysm formation due to acute infarction, with subsequent fibrosis and loss of paradoxical motion. Although this change in mechanical function of the involved tissue is carefully detailed, it is not clear that any specific therapy will beneficially alter this sequence of events. Whether newer medical therapy for heart failure, such as vasodilator drugs, will lessen the need for aneurysmectomy or provide a better medical prognosis is

uncertain, but does not appear likely in view of the profound disturbances of coronary anatomy and ventricular function. The fact that many of these patients have mitral regurgitation, however, suggests that vasodilator drugs might be appropriate medical therapy to consider. This is important because the average increase in cardiac output with vasodilator drugs in mitral regurgitation has been in the range of 50 percent.[3]

The data on ventricular function indicate that some measurements of resting hemodynamics, such as cardiac output, may be within the normal range. Furthermore, only cardiac index was statistically different between those groups with a good and those with a poor subsequent prognosis. Postoperative ventricular function studies, in general, showed no major improvement in hemodynamic function. It should be pointed out, however, that resting measurements of function are often not as revealing as measurements obtained during cardiac stress. Therefore, measurements following some stress, such as that produced by acute hypertension or exercise, would have been preferable in characterizing the ventricular reserve of these patients before and after aneurysmectomy.[4]

Despite little change in hemodynamics postoperatively, many of these patients were symptomatically better. This probably relates to improved ventricular reserve, although this was not specifically tested. In the past, it has been suggested that reduction of wall stress by reduction of heart size due to the Laplace mechanism may improve the function of the remaining normal muscle and, therefore, provide better ventricular reserve. Precise studies on this point are lacking, but it is probably an important factor in the improved exercise capacity that many of these patients exhibit clinically. Relief of ischemia may also play a role, both by reduction of myocardial oxygen demand and also by improved flow to certain areas consequent upon bypass grafting.

The indications for operation have basically not changed over the years. Unfortunately, the long-term prognosis is a very poor one indicative of the severity of the underlying coronary artery disease and ventricular function. The inhospital mortality of 6.6 percent represents excellent surgical results in this group of extremely ill patients. The lack of long-term beneficial effect is disheartening, however, and is similar to the subsequent prognosis of patients who survive power failure following myocardial infarction.[5] Whether interventions such as intraaortic balloon counterpulsation, vasodilator therapy, or mapping and excision of ectopic foci (to eliminate arrhythmias) will modify the development of aneurysms or provide alternative therapy for the associated complications is unclear, but deserves further investigation.

WILLIAM W. PARMLEY, MD
Professor of Medicine
Chief, Cardiovascular Division
School of Medicine
University of California
San Francisco

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Special Editorial

Radiology and the Algorithmic Approach to Medicine

THE HIGH EXPENSES for medical care in the United States have caught national attention and have been the subject of numerous newspaper articles, editorials and television spectaculars. Although the Gross National Product (GNP) of the United States has risen dramatically in the last two and a half years, the cost of medical care has been increasing even faster, almost doubling its percentage of the GNP since 1950 and reaching a level close to $140 billion in 1976.[1] This amounts to almost 10 percent of the income of every American. These expenditures continue to rise at a pace double that of inflation. Many factors contribute to this: increases in wages, in personnel fringe benefits, in building costs and, among others, in the cost of advances in technology. Physicians' fees have kept pace with the general rise of health service expenditures, staying at a level of about 20 percent of the total for the last 15 years.[2]

In the last ten years there has occurred an explosive growth of medical technology, due in

great part to the spillover from space technology and spurred on by the retrenchment of that program. This later development freed many physicists and engineers to apply their talents and experience to the field of medicine. The advances have been most impressive in the application of computers to nuclear medicine and diagnostic roentgenology, as well as in ultrasonography—where the development of the gray scale B mode has greatly improved the diagnostic capabilities of this method. The dramatic developments in computed tomography (CT) simultaneously have aroused the imagination of the public, the interest of physicians, the wrath of health planners, and the enthusiasm of lay hospital boards (many of whom saw in these sophisticated machines a way of filling the beds of their institutions at the expense of the less swiftly moving neighboring hospitals). This has resulted in rapid proliferation of CT scanners, an event that regional regulating agencies have only slowed down. Yet CT scanners are just one of the expensive modalities in equipment in a radiology department today. Biplane angiographic machines cost as much as CT body scanners, and the cost of the whole array of equipment in radiology departments, when ultrasound and nuclear medicine machines are included, is four to five times greater than ten years ago.

Because it is unlikely that the increased sophistication and cost of equipment have resulted in a proportional improvement in health care, it is understandable why agencies regulating medical care are alarmed. The United States economy will have difficulty supporting a continued rapid increase in medical care expenditures. Yet it can be predicted that the American public will not willingly give up the advances in medical care. It is almost impossible to cut the cost of medical services to any great extent without radically changing our social and economic ways; it is imperative, therefore, to render economies by increasing efficiency and eliminating unnecessary procedures. Because diagnostic workups frequently involve duplication and costly traditional routine steps, and represent a large part of the expenditures, an algorithmic rational approach to diagnostic workups is one of the few alternatives left to the medical profession.

The term algorithm used in this frame of reference means a set of rules for obtaining a specific output from a specific input. When these rules are followed, each step in the sequence logically leads to the next. In order to employ radiological procedures in a logical and efficient way radiologists and their clinical colleagues *must* jointly develop a set of algorithms that will guide the diagnostic workups of their patients. In the orderly progression of these diagnostic tests, the examinations to be carried out will be based on the results of those preceding them. It is important that these algorithms be reviewed frequently and changed when experience and newer advances dictate. Radiologists and clinicians, and in teaching hospitals they and the house staff, should meet during the progress of workups of their patients and jointly apply the algorithms and deviate from them, if necessary, only after discussion. Hospital patient care committees should make sure that such algorithms are in existence, that physicians are familiar with them, and that deviations are not based on the capricious prejudices of prima donnas.

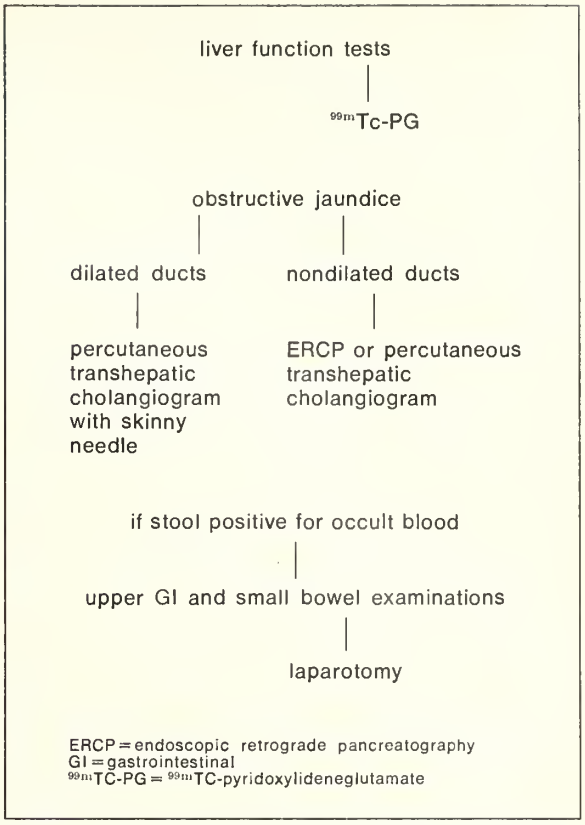

Figure 1.—An algorithm for the radiologic approach to the evaluation of obstructive jaundice (see text for explanation).

Examples of Algorithms

An algorithm for the radiologic approach to the evaluation and diagnosis of obstructive jaundice is shown in Figure 1.[3] It is applicable only

to large institutions that have CT and ultrasonographic equipment. Ultrasound is usually the best, fastest and least expensive approach for showing dilated bile ducts. In the presence of ascites, or large amounts of intestinal gas, CT scanning is more reliable. This latter method, however, is of less value than ultrasonography in cachectic patients because CT scanning depends on the presence of intraabdominal fat to outline the organs and masses. Endoscopic retrograde pancreatography (ERCP) may be employed as an alternative to percutaneous transhepatic cholangiography with a skinny needle when the biliary radicles are shown by CT or ultrasonography to be normal, or when it is important to study the pancreatic ducts. If no skillful endoscopists are available, percutaneous transhepatic cholangiography should still be attempted; it has been shown to be increasingly successful even with nondilated ducts. The upper gastrointestinal barium sulfate examinations should be carried out only if tests of stool specimens for occult blood are positive, in order to uncover invasion of the duodenum.

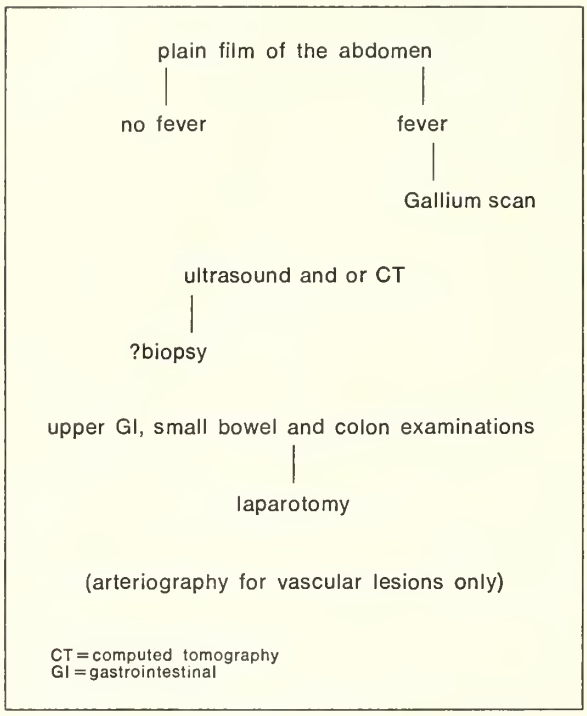

Figure 2.—An algorithm for the diagnosis of an upper central abdominal mass (see text).

An algorithm for the diagnosis of an upper central abdominal mass is shown in Figure 2.[4] The plain film examination should be the initial radiologic step. In those patients with signs of infection a gallium scan should be done to locate an abscess. Upper gastrointestinal and small bowel examinations, as well as a colon examination, should be carried out. Ultrasound and CT examinations are indicated in these patients. Ultrasound, though offering less detail, has the advantage of parasagittal as well as transverse scans and should be used as a localizing procedure that may obviate the need for a CT scan. Arteriography, which until recently was regularly done in the workup of such patients, should now be done to study only vascular lesions.

An algorithm for the diagnosis of massive rectal bleeding is shown in Figure 3.[5-7]. This algorithm is not controversial, but because patients with this condition usually present as acute emer-

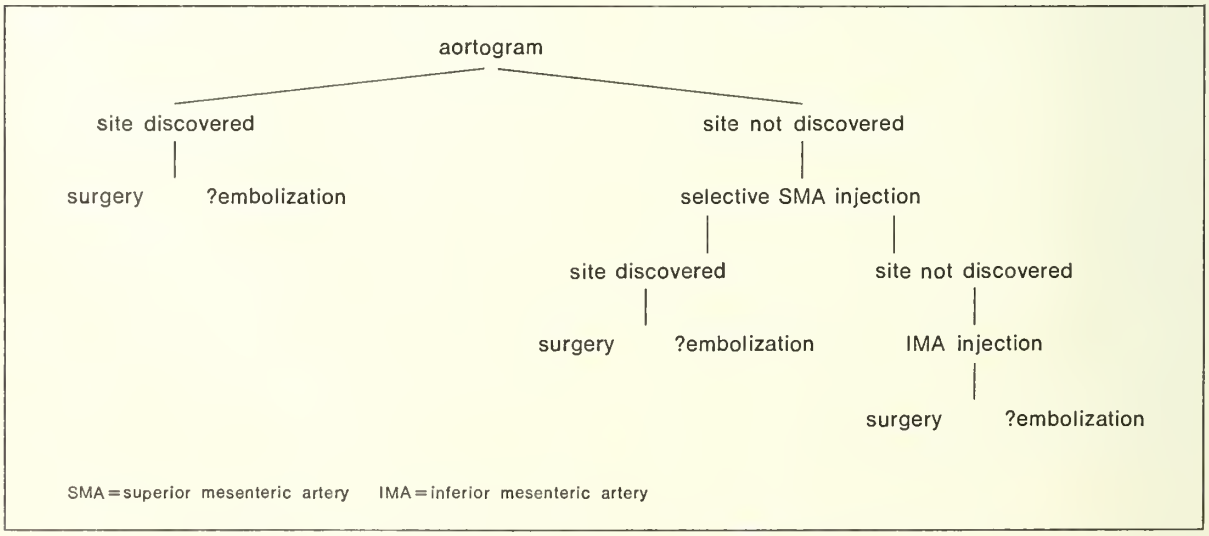

Figure 3.—An algorithm for the diagnosis of massive rectal bleeding (see text).

gencies it is important to have this approach as a guide for expeditious and prompt handling.

If physicians, surgeons and radiologists do not develop and employ a logical set of diagnostic workup procedures, nonmedical administrators will impose rules on them that will be far less informed and less flexible, and will not serve their patients well.

ALEXANDER R. MARGULIS, MD
Professor and Chairman
Department of Radiology
School of Medicine
University of California
San Francisco

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Editorial Essay

Where Is Mandatory CME Taking Us?

"WHERE IS MANDATORY CME TAKING US?" Now that continuing medical education has become mandatory in many places in the United States, it would seem incumbent upon medical educators to make mandatory CME a useful experience for physicians and a response which will satisfy the public demand for assurance of quality in patient care. These are times of increasing emphasis on public accountability in virtually every aspect of patient care, and if this cannot be accomplished through mandatory CME to the satisfaction of the public, then one may be sure that some other approach will be mandated. Since other approaches are likely to be more difficult and possibly less consistent with what physicians are doing, or ought to be doing in their practice situation, it would seem that this is compelling enough reason to make mandatory CME work.

What is it the public wants? It seems that the public wants some kind of assurance that physicians are competent to do whatever it is they are supposed to do in their practices. Unfortunately there is enough evidence that enough physicians are falling short to have brought about this demand for quality assurance on the part of the public.

The logic of mandatory CME to assure continuing physician competence seems obvious enough. Originally physicians were held to be competent to be licensed after having gone through an educational process in medical school followed by an internship and an examination acceptable to a state licensing board. Later physicians were held to be competent in a specialty after further education and further examination by a specialty board. It therefore seems logical enough to assume that if education made physicians competent in the first place then continuing medical education should assure continuing competence. This seems to be the rationale upon which mandatory CME is based and it is this assumption which we must show to be valid if mandatory CME is to work.

Now where do CME educators find themselves?

1. CME educators have committed themselves to the idea that CME works to improve patient care—that is, patient care outcomes. It certainly does this. Physicians continue to learn. Physicians do not continue to practice as they did when graduated from medical school or specialty training many years earlier. They must have learned something as they have gone along and this by definition would be CME. This is an article of faith.

2. It has frequently been said it is generally the good doctors who do formal CME, and that the problem has been that those who really need CME are not the ones who have gotten most of it.

3. These words have now been heard and some 20 states have legislated the tool of mandatory CME. In a way there is now a challenge to see if CME can be made to work to assure continuing competence. It is in a sense up to CME educators to prove that it can.

4. Over the years doctrine has developed somewhat as follows:

- The purpose of CME is to improve patient care, morbidity and mortality, and presumably it does;
- CME programs should be developed on sound educational principles;

- CME should result in a change in physician behavior;
- CME should result in a demonstrable improvement in patient care outcomes;
- Category 1 credit hours are the hard core of CME, that is the place where we can and do enforce our doctrine.

But some problems are now developing with this doctrine:

1. It is proving very difficult, well nigh impossible, to link CME, particularly any single CME experience, to measurable changes in patient care, although it is clear that, overall, physicians have learned a great deal since graduating from medical school and it is clear morbidity and mortality statistics have improved over the years.

2. CME educators have decided to worship at the altar of needs assessment, stated objectives, planned programs, instructional methods and evaluation—precisely the same approach that is used for a course or for educational programs in undergraduate medical education. But there are practical difficulties in fitting many kinds of worthwhile CME into this traditional mold. Could it be that this approach needs closer examination as to its appropriateness for CME which is more problem-oriented—more like adult education in both its motivation for learning, and in how this is accomplished.

3. The commitment to try to link a CME experience to the demonstrable change in a physician's practice behavior has proven difficult in practice. Could it be that physicians do not respond in knee jerk fashion as some behavioral scientists seem to expect—or even as if they were still undergraduate medical students? Could it be that physicians are taught to be critical of what they read and hear, and that they only change their practice behavior when they are convinced it will really make a difference?

4. There is no satisfactory direct evidence that CME programs influence a physician's patient care outcomes. This is not surprising when one considers that one is asking 1, 5, 10 or 20 hours of formal CME instruction on necessarily limited topics to measurably affect outcomes of perhaps several hundred physician-patient encounters in a month or several thousand in the course of a year. It really seems unrealistic to expect any immediate measurable result.

5. And finally there are problems with the Category 1 hours approach of mandated CME and the need to show that by taking a certain number of Category 1 hours of CME instruction a physician will continue to be up-to-date in his practice. At present it is simply not possible to do this.

With this focus, perhaps even this preoccupation with the now familiar rote of needs assessment, objectives, relationship to patient care, the pedagogy of instruction and evaluation in terms of physician behavior and patient care outcomes, CME educators seem to have locked themselves into a sort of ritual which focuses on a process rather than on what actually needs to get done.

This brings us to the basic question: Have the right questions been addressed? Is improvement in patient care really the immediate or proximal aim of CME, or is it more likely an ultimate benefit of what CME accomplishes over time? After all, morbidity and mortality statistics and even individual patient care outcomes generally take time to become measurable, and they are surely influenced by many other things than an educational experience of a physician in a formal Category 1 CME program.

Perhaps there may be a clue in what the public seems to be asking from CME. The public seems to want some assurance that a physician is competent to do whatever it is he is supposed to do in his practice, and looks to CME to provide this assurance. If this is true, then it would seem that CME should begin to address continuing competence as its proximal aim and pay less attention to trying to effect measurable changes in physician behavior (which may or may not actually need to be changed) or to trying to measure the effect of CME on patient care outcomes which is difficult if not impossible to do.

All of this would suggest that if mandatory CME is to work to the satisfaction of the public, it must be linked more closely to a physician's competence to do whatever it is he does in practice, and then some better method of accountability for this continuing competence should be developed, perhaps through some kind of redefinition of the use of, or finding new uses for, the Category 1 hours of instruction since this is the tool we have now been given for mandatory CME. The next step would be to assure the public in some acceptable fashion that through the mandatory CME a physician continues to be at least reasonably competent to do whatever it is he is supposed to be doing in the care of his or her patients.

Some of the key issues appear to be the following:

1. Is the "planned program" as presently promulgated by the American Medical Association and others really the best approach? Are there substantive differences in the most effective educational approaches for physicians at the undergraduate, postdoctoral and practitioner levels? If so, what are the differences? Are we trying to put on a shoe that does not fit?

2. What is really meant by physician competence? Is cognitive knowledge enough, or are certain practice skills necessary? Should a competent physician have skills in communicating with patients—really skills in the doctor-patient relationship? Are cost considerations important for a competent physician, are records and accountability, and are general management skills important components of physician competence? And is patient compliance and patient satisfaction important? These are some examples of what might be involved in physician competence, and if so how is mandatory CME to relate to them?

3. Competence for what? How does one define a physician's practice or practice profile? A physician may be competent as a family physician but incompetent to run a dialysis unit. Competence clearly relates to practice situations. Also consideration should be given to what physicians need to know to be competent not only in their day-to-day practice, but to what they may need to know beyond this. How about the unusual or rare case which is not often seen but should be recognized? What about the specialty as a whole, and the other subspecialties within the specialty? And what about the capabilities and limitations of all the other specialties of medicine? Clearly this should be a part of competence. Should not questions such as these be considered when one tries to relate CME to the practice profile?

4. And finally, a major challenge will be to take the tool of mandatory Category 1 credit hours and somehow redefine and restructure this tool so it can indeed become an instrument through which CME can be more closely linked to continuing competence in a physician's practice, and so give the public some greater assurance than we are able to do now that a physician is indeed competent to do whatever it is he or she is supposed to do in practice.

Mandatory CME is clearly taking us in new directions. It is posing new challenges to CME educators and CME administrators. If these challenges can be met, CME can become an effective means of assuring a physician's continuing professional competence in practice.

MALCOLM S. M. WATTS, MD
Director, Extended Programs in Medical Education
School of Medicine
University of California
San Francisco

CASE REPORTS

Refer to: Smith JW: Hypoplastic right ventricle with eosinophilic endomyocarditis and patent foramen ovale. West J Med 129:64-67, Jul 1978

Hypoplastic Right Ventricle With Eosinophilic Endomyocarditis and Patent Foramen Ovale

JAMES W. SMITH, MD
Boise, Idaho

CONGENITAL HYPOPLASIA of the right ventricle with normal tricuspid and pulmonic valves is an uncommon cardiac malformation.[1] Isolated right ventricular hypoplasia with atrial septal defect or patent foramen ovale has been cited in scattered case reports. In all of these the patients were infants, young children or young adults.[2-4]

Eosinophilic leukemia with fibrosing endocarditis is an uncommon and somewhat controversial entity.[5] A number of cases with eosinophilic leukemia have been reported with changes in the endocardium associated with superimposed mural thrombi.[6,7]

In the unique case reported here, a man with congenital right ventricular hypoplasia had apparent normal cardiac function until adulthood when he was found to have probable eosinophilic leukemia. Subsequently there developed a large amount of mural thrombus in the right ventricle which led to functional tricuspid inflow obstruction and a large right to left cardiac shunt through a patent foramen ovale.

Report of a Case

A 62-year-old man presented to the emergency room with complaint of increasing dyspnea of approximately ten days duration. The patient stated that he had always been in good health with no previous hospital admission or significant illness except for a bout of vague abdominal discomfort and diarrhea five months earlier which had led him to see his physician. At that time routine evaluation had elicited hepatosplenomegaly, and a complete blood count showed a leukocyte count of 55,000 with a hemoglobin value of 14.8 grams per dl and normal platelet count. A leukocyte alkaline phosphatase score was 12 (normal, 16 to 70), and findings on a bone marrow examination were consistent with the diagnosis of chronic myelogenous leukemia with a positive Philadelphia chromosome. Plans for outpatient therapy were drawn; however, the patient demurred and did not return for further medical evaluation or therapy.

The patient remained asymptomatic until the onset of dyspnea on exertion and fatigue described at his emergency room visit. On questioning, he noted that he had had acrocyanosis for two days before presenting in the emergency room and had lost approximately 10 to 20 pounds over the previous two years. In the emergency room the leukocyte count was 88,000 with 45 percent mature eosinophils, 26 percent mature segmented neutrophils, 6 band forms, 4 basophils, 8 lymphocytes and 10 promyelocytes. The hematocrit reading was 40 percent with a hemoglobin value of 13.8 grams per dl, while electrolytes and glucose values were within normal limits. Arterial blood gas studies showed an oxygen pressure (Po_2) of 31 mm of mercury, a carbon dioxide pressure (Pco_2) of 18 mm of mercury and a pH of 7.47. Borderline cardiomegaly with clear lung fields was noted on an x-ray study of the chest. An electrocardiogram showed a sinus rate of 80 per minute with tall peaked P-waves in leads II, III and AVF, diagnostic of right atrial enlargement. An intraventricular conduction defect and nonspecific ST and T changes were also present.

On physical examination the patient was afebrile with a regular pulse of 86, blood pressure of 140/80 and respirations of 30 with obvious dyspnea. He was responsive to questions and able to give historical information at the time of his admission. Examination of the neck showed there to be jugular venous distension without visible pulsations and an estimated central venous pressure of 20 cm of water. Pulmonary examination showed the lungs to be clear. On cardiovascular examination a regular rhythm was noted with a left parasternal lift but no thrill. Auscultation

Dr. Smith is in private practice.
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Reprint requests to James W. Smith, MD, 220 North First Street, Boise, ID 83702.

showed a grade II/VI midsystolic murmur, best heard in the 2nd to 3rd left interspaces along the sternal border. A midsystolic click could be heard over the left parasternal area. No S3 or S4 was present and no diastolic murmurs were apparent. On abdominal examination a notably enlarged, nontender liver and spleen were noted, both palpable approximately 10 cm below the costal margins. Examination of the extremities showed moderate cyanosis of the nail beds with no evidence of edema.

The patient was initially given 100 percent oxygen by mask. When this was unsuccessful in raising the Po_2, intubation was carried out and 100 percent oxygen was administered by respirator. This maneuver produced no significant change in arterial Po_2 and the possibility of a right-to-left intracardiac shunt was considered. Cardiac catheterization was undertaken.

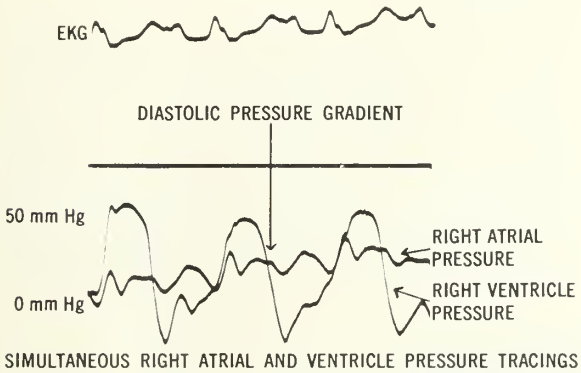

Figure 1.—Simultaneous right atrial and ventricular pressure tracings obtained by double lumen catheter across tricuspid valve. A mean diastolic pressure gradient of 10 to 15 mm of mercury was present.

Cardiac Catheterization

At catheterization, the right atrial mean pressure was measured at 25 mm of mercury. As the catheter was passed into the right ventricle, a pronounced diastolic pressure gradient was noted and passage of a double lumen catheter showed a diastolic pressure gradient of 10 to 15 mm of mercury across the tricuspid valve (Figure 1). Right ventricular pressure was 35/10 to 15 mm of mercury and pulmonary artery pressure was 32/10. Pulmonary capillary wedge pressure was 15 mm of mercury. Cardiac output was found to be 7.8 liters per minute with an index of 4.5 liters per sq meter.

Green dye studies were done and showed evidence of a large right-to-left shunt at the atrial level. An approximate 40 percent shunting of the cardiac output at the atrial level was calculated. Angiography with right atrial injection showed passage of dye across the atrial septum and into the left ventricle as well as through a very small irregular right ventricular cavity and into normal appearing pulmonary arteries. A selective injection into the right ventricle showed a small irregular partly obliterated right ventricular cavity which appeared to be filled with either a clot or a tumor mass (Figure 2).

Following catheterization, the patient was

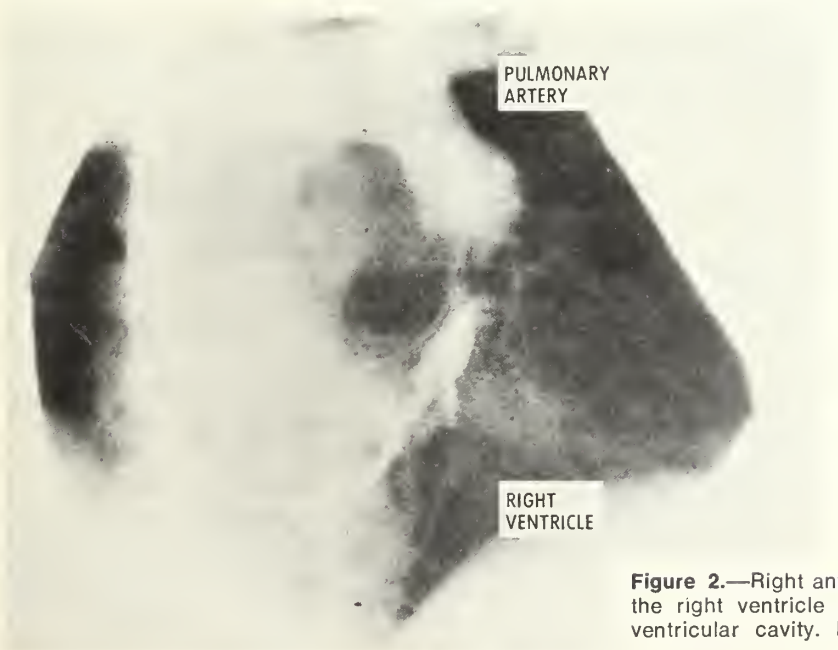

Figure 2.—Right anterior oblique contrast injection into the right ventricle shows the nearly obliterated right ventricular cavity. Pulmonary artery appears normal.

taken to surgery for an attempt to increase pulmonary artery flow and relieve hypoxemia. A Dacron® shunt was placed between the proximal ascending aorta and the proximal pulmonary artery, and a surgically created large atrial septal defect was made. At the time of operation, the right ventricle was found to be filled with necrotic yellow-tan material of a very firm adherent quality. Following the operation the patient was unable to be taken off cardiopulmonary bypass.

Findings

At autopsy, the heart was found to weigh 500 grams with an external prominent bulging right ventricle. Opening of the cardiac chambers showed the atria to be grossly unremarkable in size and shape with an opened surgically enlarged foramen ovale. The right ventricular cavity was hypoplastic, extending approximately half of the way from the right base to the true apex of the heart. It was filled with necrotic yellow-tan material which, on microscopy, was found to be organized thrombus. This material was plastered tightly against the undersides of the tricuspid leaflets creating a relatively immobile tricuspid valve (Figure 3). The leaflets themselves were not involved and, with removal of the organized clot by dissection, the tricuspid valve appeared normal.

The pulmonic valve was unremarkable; the left atrial and left ventricular chambers and mitral and aortic valves were normal. The coronary arteries showed no evidence of significant atherosclerotic obstruction. The myocardium of both ventricles appeared free of infiltration, but there was a small amount of white fibrous scarring which appeared over the distal portion of the right ventricular cavity. The endocardium of the right ventricle was thickened and had a rough, granular appearance. Pathological evaluation showed diffuse eosinophilic infiltrate of the bone marrow, liver, spleen and lymph nodes.

Discussion

Right ventricular hypoplasia is an infrequent congenital cardiac defect usually associated with abnormalities of the tricuspid or pulmonic valve ranging from mild stenosis to atresia.[8,9] Right ventricular muscular hypoplasia can occur with normally formed tricuspid and pulmonary valves, as described by Sackner and co-workers;[2] however, all previously reported cases have been in symptomatic children or young adults.

Figure 3.—Heart showing hypoplastic right ventricle with organized thrombus undergirding the tricuspid valve. Endocardial thickening and fibrosis can be seen in the region of the right ventricular apex.

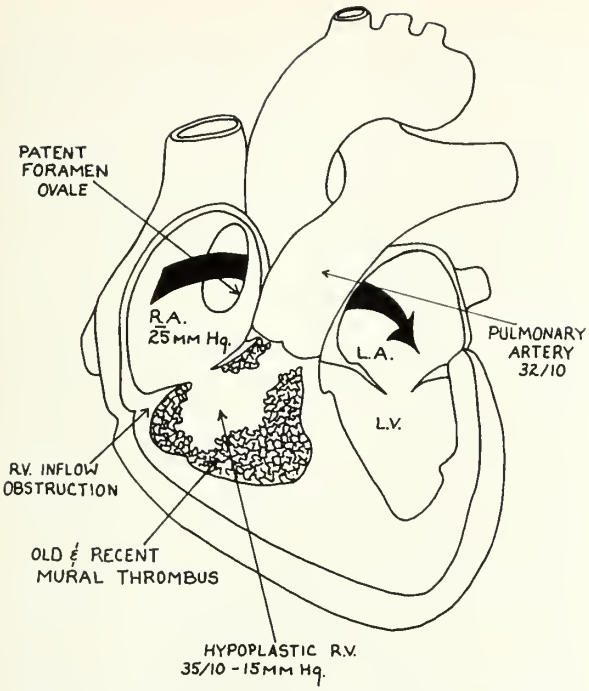

Figure 4.—Shunting through a patent foramen ovale from the right atrium (R.A.) which led to cyanosis and hypoxemia. The hypoplastic right ventricle (R.V.) is shown filled with thrombus which undergirds the tricuspid valve leading to a diastolic pressure gradient.

Our patient was a 62-year-old man who did manual labor, had worked all of his life and had no history of easy fatigability or cyanosis until approximately 20 days before his death. Therefore, it would appear that the right ventricular function had been adequate for normal activity until the onset of thrombosis in the right ventricle. This produced a compromise in the movement of a normal tricuspid valve resulting in clinical tricuspid stenosis which led to pronounced elevation of the right atrial pressure and a right-to-left shunt through a patent foramen ovale (Figure 4). Hence, it is probable that had not right ventricular thrombosis occurred secondary to the eosinophilic endomyocarditis, this man would have lived his normal life span without any suspicion of congenital heart disease.

The association of eosinophilic leukemia with endocardial changes and mural thrombi has been well established in the medical literature. The causes for the endocardial changes and for the secondary thrombus formation are unknown, but Solley and co-workers[6] noted that the most impressive changes at autopsy were in the heart. Specifically, they found mural thrombi present in left and right ventricular chambers. Benvenisti and Ultmann,[10] reviewing 48 autopsy cases, found that mural thrombi were present in 30 percent, often associated with an endomyocardial fibrosis.

It has been speculated that the eosinophils contain a substance that does damage to the endocardium, setting the stage for thrombus formation and cardiac compromise. In our patient it is very likely that the congenitally small right ventricle allowed for more rapid damage and progression of disease, leading to thrombosis only in the right side of the heart. As the thrombus propagated, the leaflets of the tricuspid valve were undergirded by this mass which prevented normal opening of the valve and created the hemodynamic feature of significant right-to-left shunting through a patent foramen ovale and the onset of dyspnea due to pronounced hypoxemia.

Summary

The unique case of a 62-year-old man is described in which a hypoplastic right ventricle, with normal tricuspid and pulmonic valves, was present. Hemodynamic function was adequate until the onset of eosinophilia resulting in endocardial damage and the propagation of a large amount of right ventricular mural thrombus which compromised the tricuspid valve. This led to the clinical features of right ventricular inflow obstruction with pronounced elevation of right atrial pressure and creation of a significant right-to-left intracardiac shunt through a patent foramen ovale. The development of symptoms of dyspnea, fatigue and cyanosis led the patient to seek medical consultation.

Cardiac catheterization with angiography showed the presence of the abnormality; however, attempt at surgical correction with creation of an aorticopulmonary window and enlargement of the atrial septal defect was unsuccessful.

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Refer to: Riddle MC, Golper TA, Fletcher WS, et al: Glucagonoma syndrome in a 19-year-old woman. West J Med 129:68-72, Jul 1978

Glucagonoma Syndrome in a 19-Year-Old Woman

MATTHEW C. RIDDLE, MD
THOMAS A. GOLPER, MD
WILLIAM S. FLETCHER, MD
Portland, Oregon

JOHN W. ENSINCK, MD
PHILLIP H. SMITH, PhD
Seattle

ABBREVIATION USED IN TEXT
IRG = immunoreactive glucagon

A NEW CLINICAL SYNDROME associated with glucagon-secreting tumors has recently been described.[1-3] The main features are a distinctive and disabling skin rash, weight loss, anemia and glucose intolerance. Most persons with the syndrome have been elderly and seriously ill at the time of diagnosis. We report here a case with typical and dramatic findings of the disorder appearing in a 19-year-old woman. Because of her youth and otherwise good health, extensive metabolic studies have been possible, and several unusual features are described.

Report of a Case

In a previously well 19-year-old woman a pruritic vesicular skin eruption developed on the ankles. Initially it subsided after therapy with orally given prednisone. The rash recurred, however, developing into a widespread eruption, worst around the genitals, the mouth and areas of superficial trauma. Glossitis was also present, as was significant emotional depression. Findings on a skin biopsy were not diagnostic. Periodic exacerbations continued despite therapy with topically administered creams, orally given prednisone, vitamins and dietary restrictions, and avoidance of contact with metals.

From the Departments of Medicine (Riddle, Golper) and Surgery (Fletcher), University of Oregon Health Sciences Center, Portland, and the Departments of Medicine (Ensinck) and Biological Structure (Smith), University of Washington, Seattle.

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Reprint requests to: Matthew C. Riddle, MD, Division of Metabolism, Department of Medicine, University of Oregon Health Sciences Center, Portland, OR 97201.

About 11 months after onset of the rash the patient reported several new symptoms, including muscle weakness, nausea, early satiety and cessation of menses. A weight loss of ten pounds, diffuse loss of muscle mass and mild anemia were noted. Glucose tolerance, which had been normal previously, was mildly impaired. Repeat skin biopsy showed epidermal cleavage forming bullae containing acantholytic cells. Fasting plasma immunoreactive glucagon (IRG) activity was 800 pg per ml, five-fold elevated, confirming the diagnosis of glucagonoma. Visceral angiography showed a small pancreatic tumor and many liver metastases. Further medical evaluation uncovered no other noteworthy findings. The only medical history worth noting was a moderately severe depression three years before. Her mother and sister were reported to have glucose intolerance, and a maternal aunt to have overt diabetes. Extensive laboratory studies showed the following abnormal findings: hemoglobin, 10.2 grams per dl; hematocrit, 31 percent; leukocyte count, 3,700 with relative lymphocytosis; plasma parathyroid hormone, 84 μlEq per ml; while calcium was 9.3 mg per dl, with the normal range up to 82 μlEq per ml (Nichols Institute, Portland, Oregon); fasting plasma insulin, 17 to 30 μU per ml. Plasma amino acids concentrations were mostly depressed, especially those of ornithine, threonine, asparagine/glutamine, valine and alanine, which were below half of normal values. Results of liver function tests were within normal limits.

When the diagnosis was established dietary restrictions were removed and the rash concurrently improved. After informed consent, pretreatment physiologic studies were done, followed by excision of all primary tumor tissue and chemotherapy of metastases with intravenous administration of tubercidin (1.5 mg per kg of body weight), and 5-fluorouracil (1 gram per day for eight days) by hepatic arterial infusion. After an initial exacerbation the skin rash disappeared and most of the lost weight and muscle mass was regained; the patient's sense of well-being returned. Fasting plasma IRG fell by half, to 300 to 400 pg per ml, and insulin to 5 to 20 μU per ml. Chemotherapy has continued: Intravenously given tubercidin, 1.5 mg per kg of body weight every one to two months, and orally or intravenously given 5-fluorouracil, 750 to 1,000 mg a week, supplemented with 1 gram per day given intravenously for two to eight days coinciding with tubercidin doses. Placement of a femoral

arteriovenous (umbilical vein biograft) shunt has facilitated chemotherapy. The remission has lasted 31 months to date.

Methods

Immunoreactive glucagon was assayed using the Unger 30K antibody, usually after removal of large molecular weight species (over 3,500 daltons) in plasma by acetone precipitation.[4,5] Plasma IRG activity was fractionated on a column of Bio-gel P-10 calibrated with proinsulin, insulin, glucagon and tritiated water. Insulin was assayed by the method of Zaharko and Beck,[6] and glucose by glucose oxidase. Dynamic studies of plasma glucose, insulin and glucagon responses to various stimuli were carried out after an overnight fast, each on a separate day. Standard commercial preparations of oral (Koladex) and intravenous (Cutter) glucose, regular insulin (Squibb), tolbutamide (Upjohn), epinephrine (Parke-Davis) and diazoxide (Schering) were used. Casein hydrolysate (Mead-Johnson) and vegetable oil (Wesson) were used for oral loading studies. Tissue was fixed in neutral formalin and Bouin's solution for light microscopy, and in glutaraldehyde for electron microscopy. Tumor sections were stained with hematoxylin and eosin, aldehyde fucsin, and the silver impregnation methods of Grimelius[7] and Hellerstrom and Hellman.[8] Immunofluorescence studies of primary tumor and adjacent normal pancreas were done by the indirect technique,[9] using anti-insulin serum, 30K rabbit antiglucagon serum, and rabbit antisomatostatin serum (a gift of Dr. B. L. Baker, University of Michigan).

Results

Studies of Circulating IRG

IRG activity in unmodified fasting plasma at the time of diagnosis was 800 pg per ml. Activity in acetone extracts was 600 pg per ml, suggesting that only about 25 percent of the total was accounted for by high molecular weight material excluded by the extraction procedure. Fractionation of unmodified plasma by column chromatography verified this inference, showing 70 percent of IRG in species of molecular weight approximating that of normal glucagon (3,500 daltons). Most of the remaining IRG eluted in an area corresponding to molecular weight of 8,000 to 12,000 daltons. IRG assay in all subsequent studies was done on acetone extracts.

Physiologic Studies

Results of several standard physiologic studies done before treatment are shown in Table 1. Little or no suppression of plasma IRG occurred following oral administration of glucose, intravenous administration of glucose or immediately after injection of insulin. No clear response in IRG followed insulin-induced hypoglycemia. In contrast, a quick rise in IRG immediately followed intravenous administration of tolbutamide, the elevation persisting an hour. Tolbutamide injec-

TABLE 1.—*Responses of plasma glucose (mg per dl), plasma immunoreactive glucagon (pg per ml) and plasma immunoreactive insulin (μU per ml) to various stimuli before surgical therapy or chemotherapy.*

Oral glucose 100 grams	Baseline	30 min.	60 min.	90 min.	120 min.	180 min.	
Glucose	91	218	191	155	121	86	
IRG	504	513	473	382	416	456	
Intravenous glucose 25 grams	Baseline	2 min.	5 min.	10 min.	20 min.	40 min.	60 min.
Glucose	77	..	..	276	246	204	163
IRG	620	810	760	660	500	550	410
IRI	22	224	184	152	252	267	171
Intravenous insulin 0.2 unit per kg	Baseline	10 min.	20 min.	30 min.	40 min.	50 min.	60 min.
Glucose	58	41	34	14	22	39	82
IRG	550	680	540	480	770	660	550
Intravenous tolbutamide 1.0 grams	Baseline	2 min.	5 min.	10 min.	20 min.	40 min.	60 min.
Glucose	72	..	..	75	73	59	46
IRG	590	1,070	850	860	730	720	800
IRI	26	105	115	122	118	83	50
Intravenous epinephrine 6 μg per min. continuously	Baseline	15 min.	30 min.	40 min.			
Glucose	71	75	125	137			
IRG	510	1,490	830	1,260			
IRI	25	12	53	25			

IRG = immunoreactive glucagon IRI = immunoreactive insulin

tion is reported to lower plasma IRG under normal conditions.[10] IRG also increased during continuous epinephrine infusion.

The response of plasma IRG to ordinary mixed meals over 24 hours also was studied preoperatively (Figure 1). A prominent rise in IRG followed each meal, subsiding to the basal level before the next meal. Insulin responses were very brisk. Because of these results, three further studies were done postoperatively to identify what component of meals was responsible (Figure 1). Baseline IRG concentration was lower in the posttreatment studies, when tumor hormone derived only from metastatic tissue. A 500 ml water load failed to provoke any response of glucose, insulin or IRG. Gastric distension consequently seemed not to account for the IRG response. In contrast, meals of casein or vegetable oil were followed by large increases of IRG. In each case plasma glucose rose as well. The hyperglycemia after fat ingestion suggested biological activity of the elevated IRG. The prominent rise of plasma IRG after meals was considered possibly harmful, and possibly susceptible to drug blockade. Therefore, studies of plasma IRG response to a standard mixed lunch after no pretreatment, pretreatment for one day with 100 mg of diazoxide given orally every eight hours, and pretreatment with diphenylhydantoin (100 mg given orally three times a day for several weeks) were carried out. No clear suppression of postprandial IRG occurred with either drug.

Tumor Pathology

The primary tumor was a 2.5 cm cystic nodule. With hematoxylin and eosin staining both primary and metastatic tissues showed morphology typical of islet cell carcinomas. Both failed to show selective staining for A or D cells when examined with the methods of Grimelius[7] and of Hellerstrom and Hellman.[8] Immunofluorescence studies showed glucagon immunoreactivity in many but not all tumor cells, but failed to show either insulin or somatostatin. Studies of adjacent normal pancreas validated the methods used, showing the usual immunofluorescence pattern of these hormones. Tumor content of IRG measured in acid ethanol extracts was 3.2 μg per gram wet weight in primary, and 0.3 μg per gram in metastatic tissue.

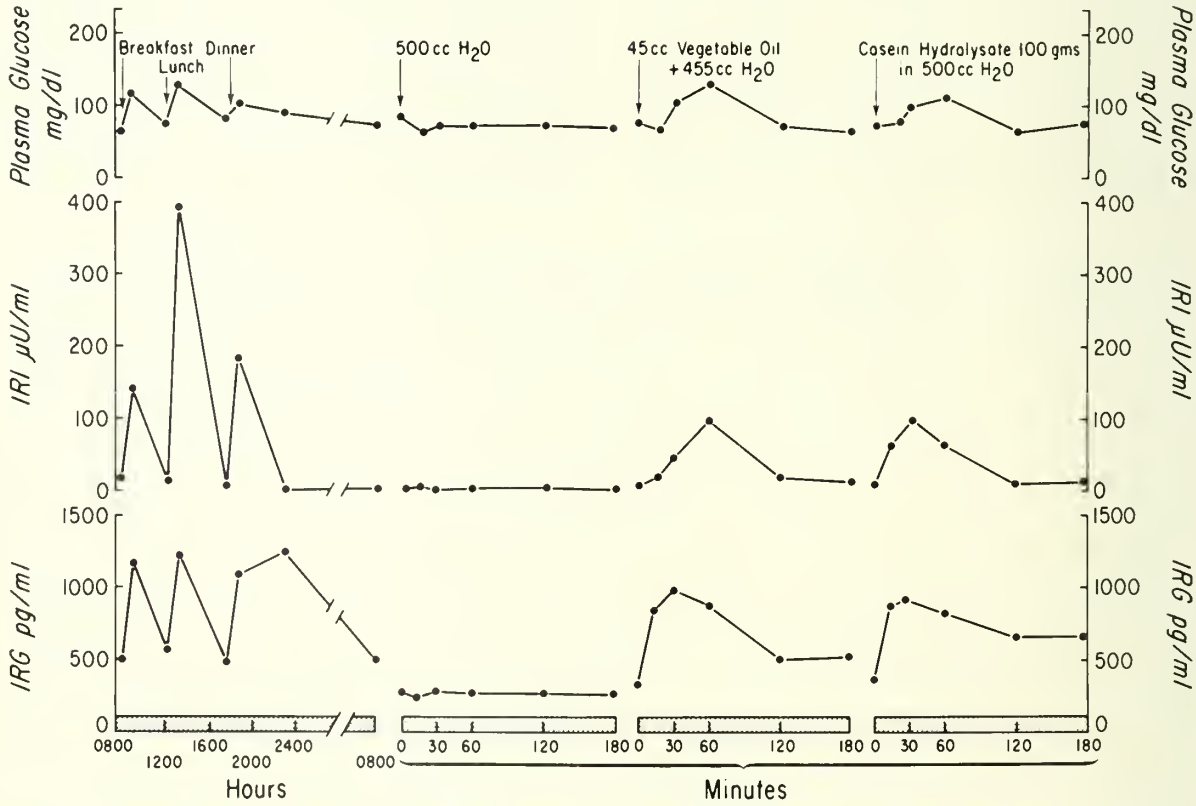

Figure 1.—Responses of plasma glucose, immunoreactive insulin (IRI) and immunoreactive glucagon (IRG) to mixed meals, water, vegetable oil and casein, all given orally. The latter three studies were done after treatment. IRG was assayed after acetone extraction, and the stippled area denotes the normal range of up to 120 pg per ml.

Cells of the primary tumor were not homogeneous to electron microscopy. In some areas cells with granules typical of A cells were seen, while in others, cells contained dense homogeneous 100 to 200 nm granules lacking a halo. In other areas few secretion granules of any type were seen. The cells containing the small granules resembled the second cell type in the glucagonoma described by Leichter and colleagues.[11]

Discussion

Most reported patients with glucagon-secreting tumors causing systemic effects have been over 50 years old, though a few reports describe younger patients with some features of the syndrome.[12-14] This case verifies that the full syndrome does occur even in the second decade of life. Since this woman was otherwise healthy her course clearly traces the early natural history of the disorder. The rash came first, followed by a recurrence of previous emotional problems. Weight loss, weakness, anemia and glucose intolerance were recognized a year after the rash developed. Like other patients with the syndrome, she had persistent hyperglucagonemia, hypoaminoacidemia and mild hyperinsulinemia. Plasma IRG suppressed subnormally with oral and intravenous administration of glucose. An immediate and sustained increase of IRG followed intravenously given tolbutamide. Insulin hypoglycemia did not elicit the usual increase of plasma IRG. Similar findings of faulty regulation of IRG secretion have been documented in other cases.[11,15-18]

Several features of this case other than the patient's youth are remarkable. One is the high proportion (70 percent) of circulating IRG activity present in a fraction corresponding to normal molecular weight glucagon. The rise in plasma glucose coinciding with the rise in IRG after fat ingestion suggests this material has high biologic potency. The rather sluggish decline in glucose after tolbutamide also suggests this, since the insulin response was normal. These findings contrast with other experience,[18-20] which suggests that the plasma of glucagonoma patients typically contains a relative excess of IRG of molecular weight of 8,000 to 12,000 or even higher, probably of decreased biologic potency. The dominance of 3,500 dalton IRG in this patient may relate to the rapid onset and severity of the clinical syndrome.

Another important finding in this patient is the prominent IRG response to mixed meals, orally given protein and orally given fat. An increase in plasma IRG after protein meals occurs in normal persons,[21] and has also been reported in a patient with glucagonoma syndrome.[18] Mixed meals and fat normally elicit only modest increases in plasma IRG.[22,23] A substantial rise of IRG after mixed meals has been described in other patients with glucagonoma,[11-15] but this appears to be the first demonstration that fat can also be a tumor IRG secretagogue. Possibly a gut factor mediates this response.[24] The effect of meals on plasma IRG may have clinical importance for this patient. We have recommended a diet with 60 to 70 percent of calories as carbohydrate and 15 to 20 percent each as fat and protein, to minimize the postprandial IRG surge. She reports that this diet is more palatable, with less early satiety.

The tumor histology also merits comment. Heterogeneity of cell types in islet cell tumors is recognized, and in this patient was evident both by electron microscopy and glucagon immunofluorescence. This finding strengthens the suspicion that these tumors often produce more than one humoral factor.[25] Also noteworthy is the absence of insulin and somatostatin from the tumor. It is suspected that both normally suppress and modulate glucagon secretion,[26,27] and that this process requires close contact between the several secretory cells in the normal islet. Perhaps the abnormal rises in plasma IRG after various stimuli in this patient reflect lack of both suppressive hormones in the tumor.

Finally, the apparent persistence of biological actions of IRG in this patient argues against glucagon's effects being entirely evanescent. Some evidence suggests that the hyperglycemic effect of physiologic hyperglucagonemia is transient.[28] Despite this, our patient had mild but progressive glucose intolerance, fasting hyperinsulinemia and a rise in glucose after a rise in IRG provoked by oral fat. In other cases similar carbohydrate intolerance associated with glucagonomas has been seen.[29] While indirect, this evidence suggests that the hyperglycemic effect of persistent hyperglucagonemia in the range found in this patient may be of long duration.

Summary

A case of the glucagonoma syndrome in a 19-year-old woman is described. During a year, severe dermopathy, depression, weight loss, anemia and mild glucose intolerance developed, lead-

ing to recognition of a metastatic islet cell tumor. Fasting plasma immunoreactive glucagon (IRG) was 800 pg per ml, and 70 percent of this consisted of normal (3,500) molecular weight IRG. Faulty regulation of plasma IRG included pronounced increases after mixed meals and orally given fat. Tumor cell morphology was heterogeneous, and while glucagon immunofluorescence was shown, insulin and somatostatin immunofluorescence were lacking. A clinical remission was induced and sustained by surgical therapy and chemotherapy. The case documents the occurrence of this syndrome in the second decade of life, a favorable response to palliative therapy, and a relationship between meal composition and plasma IRG that may have clinical importance for this patient.

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Idiopathic Acute Interstitial Nephritis

MARK L. GRABER, MD
Boston

MARTIN G. COGAN, MD
DAVID G. CONNOR, MD
San Francisco

ACUTE INTERSTITIAL NEPHRITIS (AIN) must be considered in any patient presenting with acute renal failure; the pathologic inflammation may resolve and the prognosis is generally favorable. Previous reports emphasize that AIN with acute renal failure is most frequently seen as a manifestation of drug hypersensitivity, or rarely in association with overt infection. We report the case of a patient with reversible acute renal failure and biopsy-confirmed AIN in whom none of the known pharmacologic or infectious associations of AIN were identifiable. Fluorescent antiglobulin studies showed intense interstitial staining for IgM, with staining of both tubular and glomerular basement membranes for IgG, IgM and complement. We believe that the AIN in this case may represent virus induced immunologic injury.

Report of a Case

A 36-year-old woman, a schoolteacher, had a three-week illness characterized by fatigue, low grade fever, nasal congestion, cough and mild diarrhea. Findings on physical examination were

From the Department of Medicine, Mt. Zion Hospital and Medical Center, San Francisco. Dr. Graber is now with University Hospital, Boston.

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Reprint requests to: Mark Graber, MD, Department of Medicine, University Hospital, 75 E. Newton St., Boston, MA 02118.

unremarkable. The sedimentation rate was 103 mm per hour and the blood urea nitrogen (BUN) was 30 mg per dl. Despite resolution of all symptoms in five days, the BUN had risen to 60 mg per dl, and the patient was admitted to hospital.

The patient had not noted pharyngitis, rash, arthralgias, photosensitivity or ocular symptoms. There was no history of flank pain or dysuria, and urinary volumes had been normal. The patient distrusted drugs, and had used none in the months before admission.

She had previously been healthy except for borderline hypertension. One year earlier, results of a complete blood count, analysis of urine and serum chemistry screen were normal, and the BUN was 12 mg per dl.

On physical examination at admission, the patient appeared healthy. Blood pressure was 140/96 mm of mercury, there was no fever and the examination showed no abnormalities.

Findings on an electrocardiogram and x-ray study of the chest were normal. The hemoglobin value was 10.9 grams per dl, the leukocyte count was 13,000 with 83 percent neutrophils, 11 percent lymphocytes, 4 percent monocytes, 2 percent basophils and no eosinophils. The uric acid, phosphorus and serum chemistries were normal. The sodium level was 134, potassium was 4.3, chloride was 96 and bicarbonate was 22 mEq per liter. The BUN was 59 and the creatinine level was 7.6 mg per dl. Analysis of urine showed a pH of 7, a specific gravity of 1.003, + + protein and + + + glucose with a simultaneous plasma glucose of 112 mg per dl. Occasional granular and white cell casts, 5 to 10 leukocytes and 2 to 4 red blood cells were seen per high power field. The 24-hour protein excretion was 800 mg, of which less than 10 percent was albumin on acrylamide gel electrophoresis. Intravenous urography showed 17 cm kidneys and no obstruction.

Coombs, antinuclear antibody and lupus erythematosus cell tests were negative. Cryoglobulins were not demonstrable. Complement (C3 and C4) levels were normal. The IgA value was 148 mg per dl (normal 60 to 330); the IgM, 268 mg per dl (47 to 147); the IgG, 1,760 mg per dl (570 to 1,900), and the IgE, 104 units per ml (normal, less than 300). Bone marrow aspirate and biopsy findings were normal. Liver-spleen radionuclide imaging showed the spleen to be grossly enlarged.

Urine and blood cultures were sterile. Rare beta hemolytic streptococcus group C was recovered from the throat. Viral and mycobacterial

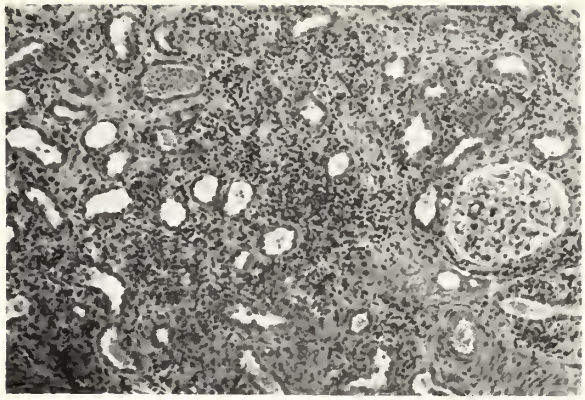

Figure 1.—Low-power view of patient's kidney showing severe interstitial nephritis and a representative normal glomerulus (reduced from ×125).

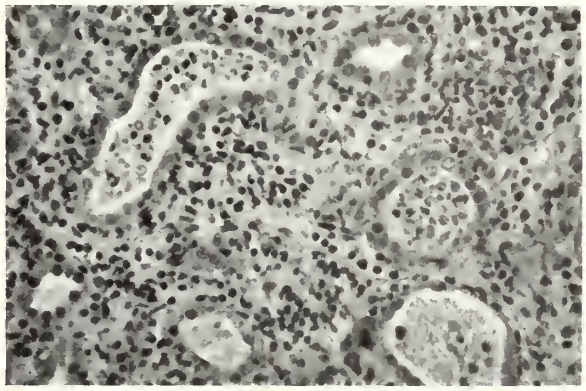

Figure 2.—Light microscopic picture showing interstitial nephritis with tubulitis (reduced from ×325).

cultures of sputum, marrow and urine were sterile. There was no reaction to intermediate purified protein derivative. A Venereal Disease Research Laboratories test and a mononucleosis screen were negative. Hepatitis B antigen was not present on radioimmunoassay, and there was no rise in the convalescent titers of antibodies to leptospirosis, Epstein-Barr virus, mumps, adenovirus, influenza A or B, parainfluenza virus or Toxoplasma. An antistreptolysin O titer was normal. Heavy metal screens were negative.

Percutaneous renal biopsy showed the histologic features (Figures 1 and 2) of AIN. The interstitium was densely packed with lymphocytes, plasma cells and rare eosinophils, and there was no evidence of fibrosis. Focal tubulitis was present. All 24 glomeruli were normal in appearance on light microscopy. Electron microscopy confirmed the tubular injury, and showed in some glomeruli extension of mesangium into the subendothelial space. Electron-dense deposits were absent. Findings on immunofluorescent

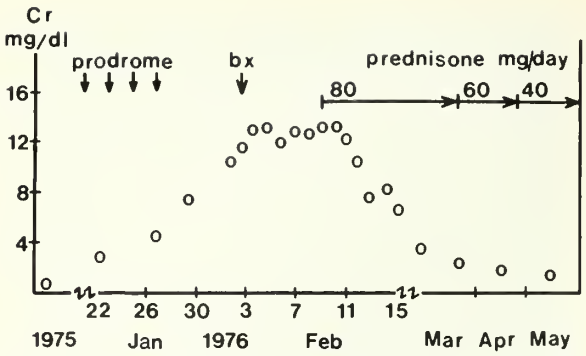

Figure 3.—Clinical course of patient showing progressive improvement in renal function following onset of prednisone therapy.

studies were most remarkable for prominent diffuse interstitial staining for IgM. Intense depostion of IgG, IgM and C3 was observed along both glomerular and tubular basement membranes. The staining was predominantly linear, with some areas suggestive of a granular overlay.

The clinical course is diagramed in Figure 3. The creatinine value initially rose one mg per dl per day, associated with progressive acidosis, hyperkalemia, hyperphosphatemia and return of the blood pressure to normal levels. Urinary output ranged from 2 to 3.5 liters per day, and glucosuria persisted. Despite progressive azotemia, the patient remained free of symptoms, her weight was stable and the results of physical examination were unchanged. After the creatinine had stabilized at 13 mg per dl, prednisone therapy was instituted at 80 mg per day. The creatinine value fell to a level of 2 mg per dl over five months.

Comment

Several features of our case are typical of AIN-induced acute renal failure. The urinary sediment was benign, the biopsy was characteristic and clinical recovery was seen. The renal failure in our patient was of the nonoliguric type, previous reports recording urinary volumes ranging from several liters per day[1,2] to anuric levels.[3-6] Eosinophilia[7] and elevated IgE,[8] common findings in drug-associated AIN, were not present. The renal biopsy showed classic changes[7,9] of AIN: tubulitis accompanied a dense interstitial infiltrate of lymphocytes, plasma cells and eosinophils. Glomerular changes were minimal, as reported in other cases,[1,6,7,10-13] and were shown only by electron microscopy.

There was no history of drug exposure, nor could infection with Toxoplasma, spirochetes, bacteria or mycobacteria be shown present. As suggested by the prodromal illness, the splenomegaly, the elevated IgM and the similarity of this patient's illness to that described with viral-associated AIN, a causative viral agent was suspected but could not be identified.

The immunofluorescence stains, showing complement and immunoglobulin along basement membranes, suggest that the renal injury in this patient was immunologically mediated. The linear immunofluorescence pattern and lack of electron dense deposits further suggests, but does not prove, that the immunoglobulin is directed against basement membrane, as opposed to originating from deposited immune complexes. Both varieties have previously been reported with AIN. The linear pattern immunofluorescence, often with hapten bound in the same distribution, has been observed with drug-associated AIN,[14-16] and linear staining has been described in a single case of AIN following poststreptococcal nephritis.[17] The granular pattern, representing immune complex deposition, has been described with the interstitial inflammation accompanying systemic lupus erythematosus[18,19] or primary glomerular disease.[20] For perspective, it should be noted that numerous groups have found no evidence of immunologic injury, as judged by immunofluorescence, in their cases of drug-associated,[7,12] viral[1] or idiopathic[17,21] AIN.

Discussion

A classification of AIN is presented in Table 1. Most cases of AIN have been associated with drug therapy; more than 100 cases have been attributed to methicillin therapy, and other agents have been sporadically incriminated. The clinical course of drug-associated AIN is fairly uniform in that evidence of hypersensitivity (fever, rash, eosinophilia) develops in the patient and progressive acute renal failure which is largely reversible is seen. The etiologic role of the drug is suggested by epidemiologic data,[22] by the presence of dermal-bound[14,17,23] or circulating[14,24] drug-specific antibody, by the presence of the drug or its metabolites bound with complement and antibody to renal tubules,[14,15,17] and most specifically by rechallenge.[3,11,25]

There is, however, reason to suspect that AIN associated with antimicrobials may be induced by the infection itself. Autopsy series in the preantibiotic era frequently noted interstitial nephritis

with bacterial sepsis,[26-28] but these early reports were often inadequate to exclude pyelonephritis, acute tubular necrosis, endovasculitis or actual parenchymal infection. More recently the case reported by Knepshield and associates[29] and the ten cases of Brass and co-workers[30] lend support to Kimmelstiel's hypothesis[31] that nonrenal bacterial infection can induce a hypersensitivity response that culminates in AIN.

Infection-associated AIN is clearly documented in cases of leptospirosis, toxoplasmosis and tuberculosis (see Table 1). Viral infections, especially mononucleosis, may also evoke AIN, with prominent glomerular injury usually present in addition to the interstitial inflammation.[32]

TABLE 1.—*Acute Renal Interstitial Inflammation**

- Acute interstitial nephritis
  - Associated with drugs:
    - Methicillin
    - Penicillin derivatives
    - Cephalosporins
    - Sulfa derivatives
    - Polymyxin
    - Antituberculars
    - Phenindione
    - Diuretics
    - Diphenylhydantoin
    - Phenazone
    - Glafenine
    - Azathioprine
    - Phenacetin
    - Phenobarbital
    - Allopurinol
  - Associated with infection
    - Bacterial
      - Streptococcus
      - Salmonella
      - Diphtheria
      - Staphylococcus
      - Brucella
      - Meningococcus
    - Granulomatous
      - Tuberculosis
      - Sarcoid
      - Mycetoma
      - Toxoplasmosis
      - Leptospirosis
      - Syphilis
    - Viruses, especially mononucleosis
  - Associated with immunologic disease
    - Transplant rejection
    - Sjögren syndrome
    - Systemic lupus
  - Idiopathic
- Secondary renal interstitial inflammation
  - Associated with primary tubular disease
    - Pyelonephritis
    - Acute tubular necrosis
    - Toxic nephritis
  - Associated with primary glomerular disease
  - Associated with vasculitis

*Documentary bibliography available upon request to authors.

Renal tubular damage mediated by immunologic injury appears to be the pathogenetic mechanism in many cases of AIN.[16,33-36] With drug-associated AIN, the inciting antigen is presumably the drug or its metabolites functioning as haptens.[14,15,37,38] In transplant rejection, AIN may result from immunity directed against autologous renal antigens.[39] Autoantigens may also evoke interstitial nephritis; this is the predominant renal lesion in Sjögren's syndrome,[40,41] and is increasingly appreciated with systemic lupus erythematosus.[18,19,21] In both of these diseases, however, the interstitial nephritis is of the chronic variety in that fibrosis is a constant feature, and renal failure, if present, is persistent.

Eight cases of reversible acute renal failure and idiopathic AIN have been reported. Three of these were described without clinical detail except to mention that iridocyclitis was present in two of them.[9,44]

In two of the five cases reviewed by Chazan and co-workers,[45] the patients had received antibiotics. The remaining three patients were middle-aged women who presented with severe renal failure and AIN on renal biopsy, and whose conditions seemed to respond to steroid therapy.

Dobrin and associates[21] reported the cases of two young women in whom acute renal failure and AIN developed following prodromal illnesses. In one there was response to therapy with systemic steroids, while in the other there was spontaneous resolution. Both had received antibiotics, but the drugs were thought to be unrelated to the development of renal failure. An immunofluorescence study in one case was negative. Complete evaluation showed no discernible cause for the renal failure, and no explanation for the uveitis and bone barrow granulomata present in both cases.

The splenomegaly in our case and the granulomatous marrow and uveal involvement in Dobrin's cases are the only features that distinguish these cases from each other. The similarities of Chazan's and Dobrin's cases and the case we report are many: all of the patients were women, and five of six had prodromal illnesses preceding the development of acute renal failure associated with AIN. Urinalysis in each showed proteinuria and microscopic hematuria. Where measured, there was no eosinophilia, the complement levels were

normal and immunoglobulins were elevated. In each case the renal failure resolved, albeit with some residual impairment.

These cases are too few in number, and the immunofluorescence data too infrequent, to postulate any common mechanism. They suggest, however, that AIN may be induced by agents besides those previously described, and these agents should be diligently sought in future cases. Clinically, the nonspecific presentation of idiopathic AIN and the favorable prognosis mandates that the diagnosis be considered in every patient with acute renal failure in whom the cause of the renal lesion is in doubt.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Prevalence of Amebiasis

To the Editor: I wish to comment on the interesting article by Hurwitz and Owen on venereal transmission of intestinal parasites [West J Med 128:89-91, Jan 1978]. Although the authors correctly quote Brooke's 1964 article from the Center for Disease Control (CDC), it is certain that the prevalence of amebiasis is now not 5 percent, nor anywhere near that level.[1]

A more recent article, also from CDC, published simultaneously with or after the article in the Western Journal, reports that amebiasis has been vastly overdiagnosed, generally because laboratory workers have mistaken granulocytes, Entamoeba coli and Entamoeba hartmanni for Entamoeba histolytica.[2] The authors make no attempt to give a true prevalence figure, but imply that previous figures may have been overstated by orders of magnitude. Of 3,500 amebiasis reports to CDC per year, at least 1,200 were apparently false positives from only three clinical laboratories. In a second authoritative article, the same authors simply state "Endemic amebiasis is rare . . . ."[3]

As an approach to the question of prevalence, or at least incidence of clinical amebiasis, I have reviewed positive cases from our hospital during the past nine years. None was seen from 1970 through 1975. Three have been seen in 765 stool specimen studies since then. Because we serve a population of about 50,000, the implied incidence might be 0.002 percent or 2 per 100,000 population per year. One patient was a homosexual man, and two were travelers returning from Indonesia and India. Other San Francisco Bay area hospitals report a similar experience: Washington Township Hospital of Fremont, 2 in 1,350 stool specimens (both from Mexican immigrants); Alameda Hospital, none in two years; Vesper of San Leandro, none in two years. I also checked with BioScience Laboratories of Van Nuys, California, which does a lot of serologic testing. They report about two positive serologies out of 120 tests done per month. Many positives are from travelers coming from Mexico.

In an area with a large, active homosexual population the incidence is probably higher than elsewhere. If the 108 cases reported to the San Francisco Department of Health actually represented all the city's 1976 cases, the incidence would be about 15 per 100,000 per year (0.015 percent).[4] None of this detracts from the conclusions of Hurwitz and Owen. Amebiasis is evidently becoming more common, and is mostly a hazard to sexually active homosexual men and to travelers. Endemic amebiasis must be extremely uncommon in the United States.

CLAUDE O. BURDICK, MD
Pathologist
Director of Laboratories
Valley Memorial Hospital
Livermore, California

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The Cause of Crohn Disease

To the Editor: In the Medical Staff Conference on Crohn disease in the May 1978 issue, Dr. J. P. Cello reviews current data hinting at infectious etiology of the illness. Dr. Cello concludes that such an infectious etiology "is not clear-cut at present but appears likely."

Contrary to this tentative conclusion of Dr. Cello and others, it seems most likely that the etiology is not infectious. I base this opinion on the lack of Crohn disease appearing in the spouse of the patient. Were the disease infectious, even considering the necessity of coexistent host factors, a higher than expected incidence would be found in the spouses. This is the case in leprosy which probably provides the best analogy. In fact,

however, the spouses are not subject to the development of Crohn disease. Blood relatives, on the other hand, are.

I think this single observation is sufficient, by itself, to dispute an infectious etiology as the prime, that is initial, cause of Crohn disease even in the presence of other co-factors.

I would appreciate Dr. Cello's commentary.

ARNOLD L. FICK, MD
San Diego, California

* * *

Dr. Cello Replies

To the Editor: With respect to Dr. Flick's letter, the absence of a significantly increased incidence of Crohn disease in spouses of patients does *not* disprove absolutely an infectious etiology to Crohn disease. If unique transmissible agents are reproducibly isolated from patients with Crohn disease but not from controls (including cohabitor spouses) the importance of host susceptibility factors must definitely be taken into consideration.

Tissue culture and *in vivo* animal studies continue to isolate unique agents from patients with Crohn disease. These agents are not seen in control populations or in patients with other inflammatory or neoplastic bowel diseases. Moreover, these unique cytopathic and histopathic agents have been serially passaged more than ten times in experimental systems.[1] These study findings certainly need further confirmation with larger numbers of patients with Crohn disease before unequivocal statements can be made. A better definition of unique inherited factors may further clarify those risk factors necessary for developing clinical Crohn disease in persons exposed to these agents.

JOHN P. CELLO, MD
Chief, Clinical Gastroenterology
University of California Service
San Francisco General Hospital

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Editor's Note

Dr. Cello raised the point that in his original article Crohn's disease was changed to Crohn disease.

The Western Journal staff for the most part uses the *Stylebook/Editorial Manual of the AMA*, Sixth Edition,[1] as the basis for the journal's editorial style. The *Stylebook* specifically notes that "eponyms are not written in the possessive form" and give Wilms tumor, Graves disease, Hodgkin disease and Ewing sarcoma among other examples.

The sixth edition *Stylebook* was selected for several reasons. One reason is well stated in the book's foreword: "A scientific journal should have a consistency of style . . . on which readers come to rely. The few rules a journal adopts should be simple, inviolable, and encourage clear, unambiguous writing."

A second reason, and more specifically to the point of why this particular stylebook was chosen, is related to the observation that the English language is continually going through a process of simplification. When two usages or forms are possible, the simpler is preferable and, in fact, usually will win out in the end (arthro-empyesis and arthro-endoscopy in the 24th edition of *Dorland's Illustrated Medical Dictionary* [1965], arthroempyesis and arthroendoscopy in the 25th edition [1974]). The sixth edition AMA *Stylebook* recognizes this "simpler is preferable" school of journalism.

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Vitamin A and Cirrhosis

To the Editor: A title should accurately reflect the content of an article, as I have noted elsewhere.[1] The report "Cirrhosis Due to Hypervitaminosis A" (West J Med 128:244-246, Mar 1978) would more appropriately have been titled "Association of Cirrhosis and Vitamin A Ingestion." The authors do not prove a cause-and-effect relation between their patient's vitamin ingestion and his cirrhosis.

The clinical findings are suggestive of hypervitaminosis A but can have other causes. Dry skin, for instance, could have been related to the patient's biliary obstruction (with consequent fat malabsorption), and cheilosis can be caused by protein deficiency, which the patient exhibited. Chronic ingestion of 40,000 units of vitamin A by an adult would be unlikely to cause hypervitaminosis A; I believe there is only one other reported case[2] with that daily intake.

The hepatic changes are likewise not specific for vitamin A intoxication. Although Hruban and co-workers[3] observed sinusoidal fibrosis, perisinusoidal accumulation of Ito cells, atrophy of hepatocytes and other changes in the patients in their two cases, they point out that most of the changes have been observed in chronic diseases of the liver other than vitamin A intoxication.

The case report mainly lacks credibility because the authors failed to obtain a serum vitamin A level while the patient was ingesting vitamin A. It is noteworthy that the serum vitamin A levels were abnormally elevated in *all* of the 17 cases reviewed by Muenter and associates.[4] Long-term ingestion of modest excesses of vitamin A (as in the present case?) would be expected to give high serum levels of the vitamin due to exhaustion of hepatic storage capacity,[4] so the missing datum is crucial.

Direct assay of vitamin A in hepatic biopsy specimens[3] might have established the diagnosis. Also, lipid-laden cells in the liver should have been examined by fluorescence microscopy for the characteristic vitamin A fluorescence.[3-5]

My own observation is that vitamin deficiencies occur far more often than is generally suspected.[6] The unfortunate effect of such an article as the present report is to make physicians leery of vitamin therapy when they should be using it more frequently. The present case report does not provide an example of the dangers of vitamin overdosage. Instead, it serves as an example of the fallacy "after this, therefore because of this."

RICHARD P. HUEMER, MD
Westlake Village, California

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* * *

Dr. Babb Replies

To the Editor: I agree with Dr. Huemer that further tests on the liver biopsy material would have strengthened the case for vitamin A toxicity. Nonetheless, for reasons stated in our paper, I remain convinced the title is an accurate one. In contrast to Dr. Huemer, my experience is that the American public takes far too many vitamins rather than too few.

RICHARD R. BABB, MD
Palo Alto, California

A 'Sign' of Inflation

To the Editor: A swallowed coin lodged in the upper esophagus will present en face on anteroposterior projections and on end on lateral projections. Aspirated coins lodged in the trachea will present just the opposite.

Upon viewing a radiograph (Figure 1) of a swallowed coin recently, my colleague, Arnold Geller, MD, observed another sign of inflation. He notes that coin denominations are going up. Kids are now swallowing quarters rather than pennies and nickels.

GARRY ROGHAIR, MD
Riverside, California

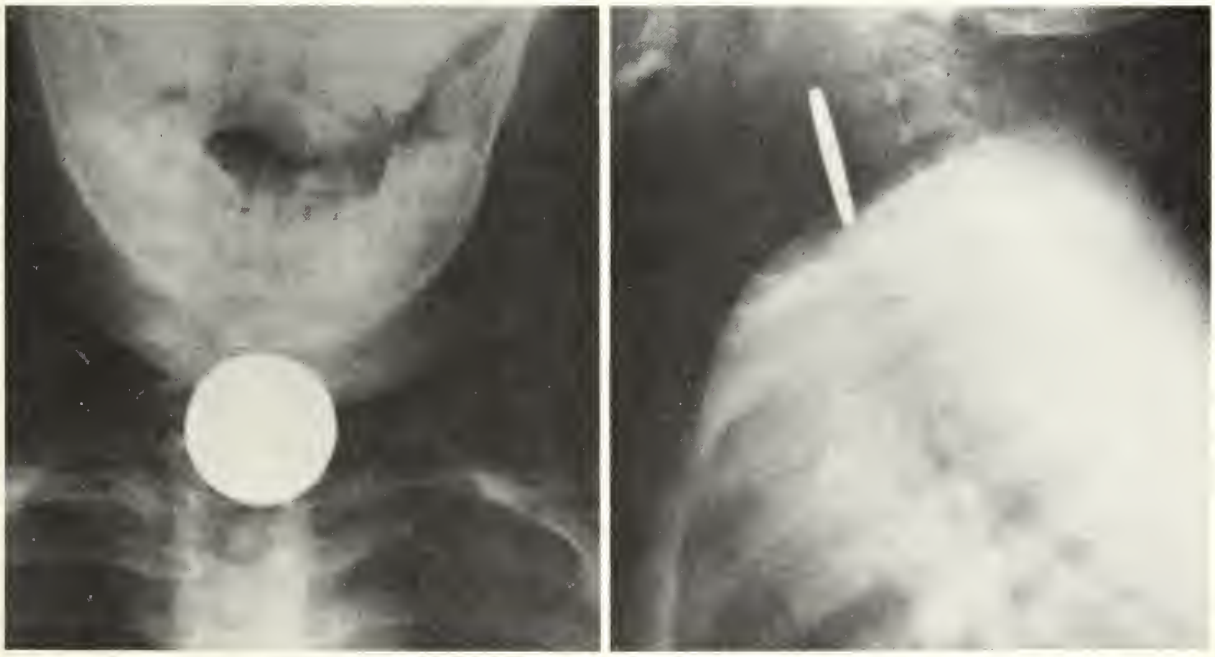

Figure 1.—Left, anteroposterior view of a swallowed coin, **Right,** lateral view.

Refer to: Gunn AE: Laetrile: Riding on something else's coattails (Commentary). West J Med 129:80-81, Jul 1978

Laetrile: Riding on Something Else's Coattails

ALBERT E. GUNN, MD, *Houston*

AT TIMES it seems that the most unimportant element in the debate over Laetrile, America's most controversial cancer nostrum, is whether it is effective against cancer or, for that matter, whether it is harmful. The argument over Laetrile is not an argument over a drug or a vitamin or a food or whatever it ultimately ends up being called. It is, rather, part of something much more profound. Laetrile is gaining approval not on what it is or does but rather because of what it represents to many people.

If I were asked who has made the greatest contribution to Laetrile's legislative success in a number of states, I would have to answer that the medical and scientific communities deserve the most credit. Laetrile's success is part of the anti-establishment mood of the country, and the establishment has had some of its legal machinery turned upon itself.

Discussions of the curative powers of Laetrile often shift gradually into complaints about bureaucrats and big-shot doctors. People are sending a message to what is loosely termed the establishment by pressuring their legislators to pass laws giving Laetrile the unique status among all drugs, vitamins and foods of being specifically legislated into legitimacy. Penicillin, L-dopa, streptomycin and polio vaccine never received such preferential treatment. This was because people were satisfied in the past to leave the medicines to the "docs." After all, physicians went to medical school to learn about these things, so people trusted their judgment. But times are changing. Now books are written about deprofessionalising medical care and people no longer believe physicians have all the answers on sickness and health.

This situation has been building for some time. It is in part a result of the increasing complexity of medical knowledge, which is mushrooming at such an incredible rate that even physicians are having a hard time keeping up. If the profession has difficulty keeping abreast, then what of the public? Rapid changes in medical care concepts must seem like irrational flip-flops to many people. What was accepted in the past—such as treating acne with x-rays—is regarded as harmful today.

If physicians keep changing their minds, some may ask, how can people put any faith in them? Well, it was not always so. In the old days physicians were consistent. They had tonics and explanations for diseases that most people could understand. Physicians spent more time talking with people over a cup of coffee in the kitchen after seeing the patient in the bed upstairs. There was not much else they could do. They watched children die of pneumonia and prescribed bed rest and whatever other remedy was available at the time and waited for the will of the Almighty.

But though they were less able to help, physicians were liked better because people knew them better. The modern physician-scientist concentrates on the disease—which he knows more about than his predecessors—and regards the body as a depersonalized system. Patients notice the difference and interpret the new attitude as

Dr. Gunn is an Assistant Director (Hospitals), University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute in Houston.

Reprint requests to: Albert E. Gunn, MD, Assistant Director (Hospitals), M. D. Anderson Rehabilitation Center, 2015 Thomas Street, Houston, TX 77009.

indifference to them as persons. The physician is not a complete villain here. In extenuation, he can plead that he is misunderstood and point out that patients are better off under the new system than they were under the old.

But, unfortunately, the increasing complexity of medical care does not completely get physicians off the hook. They still have a number of charges to answer, many of which have helped precipitate the public's ambivalent feelings toward them:

- Physicians at times appear snobbish, even supercilious. Nothing makes me wince more than listening to some big shot wearing a white coat talk down to the great unwashed on network television.
- Many physicians and scientists involve themselves in issues, particularly politics, where their say is no better than that of the man in the street. This attempt to pretend that scientific training gives one more authority to pronounce on the topics of the day makes people less likely to listen to them even when they speak about subjects in their own field. Psychiatry is still reeling from the 1,000 physicians who pronounced Barry Goldwater a nut in *Fact* magazine before the 1964 Presidential election without even examining him. They could have just told their friends that they were not going to vote for him and left the "MD" off their names. What do Goldwater's supporters—all 20 million of them—think about psychiatry now?
- Scientific studies have been overdone. Every night we hear of a new study from the medical or academic world which contradicts conventional judgments or morality. Some restraints are needed on press releases about scientific discoveries. No wonder people are leery of controlled studies.
- Doctors and scientists have been self-serving in their demands for financial support and special privileges. *Science* magazine once achieved the ultimate in this type of prattle by demanding special treatment for Andrei Sakharov because he had applied the "scientific ethos to human affairs"—whatever that means. Where was *Science* magazine when 17,000 Lithuanians imperiled their safety by protesting denial of their liberties to the United Nations. I am sure Sakharov himself does not think he is any better than they are.
- Anyone who has gone to medical school knows that a large part of the knowledge imparted is terminology: changing common English names for things to technical terms. As important as scientific terminology is in lending precision to technical journals, physicians should drop all this high-flown talk when they are explaining things to the public. I still think knee cap is better than patella.
- Scientists and others of the great washed should avoid being identified as scientists when they become involved in bizarre fads. Animal rights seems to be the latest. The neo-Malthusian scare stories about overpopulation are on the back burner now. And the supersonic Concorde has not destroyed the ozone layer yet.

Anyway, you get the point. When people write letters to their state legislators demanding that Laetrile be legalized they have something else in mind and physicians had better get the message. There still is hope because, as many times as I have heard physicians in general condemned, people still like and respect their personal physicians. The medical profession will have to build on this basic, personality-oriented faith.

The tragedy is that all this should have somehow gotten intermingled with the controversy over Laetrile as a cancer cure. Laetrile is riding this wave as a passenger. It has not made it on its own merits but is coming in on the coattails of the bigger dispute. We can only hope that not many people get hurt by it.

Refer to: Klutch M: Hospices for terminally ill patients—The California experience. (Information). West J Med 129: 82-84, Jul 1978

Information

Hospices for Terminally Ill Patients

The California Experience

MURRAY KLUTCH, *San Francisco*

IN AUGUST 1977, following its study of the philosophy and objectives of the hospice movement, the California Medical Association (CMA) Committee on Evolving Trends in Society Affecting Life made four recommendations to the governing council of the statewide medical organization:

- That the California Medical Association recognizes that, under appropriate medical supervision, the activities and efforts of qualified hospice programs constitute an appropriate role in the care of terminally ill patients.
- That the appropriate CMA committee (for example, Medical Staff Survey) . . . develop guidelines and criteria for the accreditation of hospice programs.
- That health insurance mechanisms be encouraged to incorporate provisions for hospice care in such accredited programs.
- That the [CMA's] Commission on Communications proceed with its informational program regarding hospices to the public, the profession and the health insurance industry.

The hospice concept and development that had attracted the attention of the committee had also been the subject of a resolution introduced at the spring meeting of the CMA House of Delegates. The resolution which requested "CMA to give its endorsement and approval of the ideals of hospice programs and their development by qualified individuals and organizations . . . and publicize the hospice concept . . ." happily coincided with the committee's exploration.

Faced with what appeared to be an innovative and potentially fast-growing development that reflected a humanistic approach to the care of terminally ill patients, the committee had no difficulty in convincing the governing body of the California Medical Association that the hospice concept represented not only a new level of care, but that it also had significant potential for containing the cost of care for a category of patients who were consuming an ever-increasing proporion of medical costs. For the first time in many years an opportunity presented itself in which social, medical and economic issues could be joined; in which patients' families, as well as agencies, organizations and individual persons in each community could combine forces to assist in supporting a group of patients who formerly had lacked the total support they required.

The committee's recommendation for the development of criteria and guidelines for the accreditation of hospice programs had as its background the activity of CMA's Medical Staff Survey which has a major responsibility for the accreditation of hospitals in California and whose activity has been recognized by state and federal agencies for some years. Pending the development of such criteria for hospices, a survey was conducted to identify existing operational hospice programs and those that were in the planning and organizational stages within the state of California. With the assistance of several people active on different levels of hospice organization, approximately 35 persons and organizations were initially identified with hospice programs in different parts of the state. Although there was some evidence that a number of hospitals, home health service programs, visiting nurse associations, hospital oncology and thanatology units, and community organizations had begun to offer various types of counseling services and bereavement care, the survey's concern lay primarily in identifying those programs that offered the major ingredients of hospice care: that is, those programs that identified themselves as hospices and included pain control, symptom control, emotional support, family support, and spiritual and bereavement counseling. (Organizations that serve somewhat the same function as hospices, but do not designate themselves as such, are not included in this survey.)

The use of a mail questionnaire in late February resulted in responses from 16 operational hospice programs in 11 California counties (Table 1); most of them state that their programs encompass the six basic services. Several of them

Mr. Klutch is Staff Coordinator, CMA Committee on Evolving Trends in Society Affecting Life.

Reprint requests to: Murray Klutch, CMA Committee on Evolving Trends in Society Affecting Life, 731 Market Street, San Francisco, CA 94103.

go beyond the six. In addition to the 16 which had been operational for periods ranging from two months to two years at the time of the survey, responses from an additional 11 persons, organizations or institutions in eight counties indicate that their programs are either in the planning or organizational stages (Table 2), with at least four of them scheduled to become operational sometime in 1978.

More than half of the 16 operational programs started in 1977 (see Table 3). Most of the programs are nonprofit. Of the 16 programs, 12 are nonprofit; four are profit making organizations, with one of the latter in the process of forming a nonprofit foundation for its hospice. Sponsorship of the 16 hospices is shown in Table 4.

Virtually all of the operational hospices provide the six basic services; two, however, indicated what appeared to be a lack of spiritual counseling services. Most accept patients of any age from their own areas; two draw patients from their own parent institutions. Of 15 hospices reporting, 12 stated that they admit patients with *any* terminal illness; three limit their activities almost exclusively to patients with cancer. Of the 16 responding to the question of whether physician referral is required, 11 responded affirmatively.

Of the entire group responding to a question about site of services, eight programs provide home care only, two provide inpatient care, and six provide a combination of inpatient and home care. (One hospice, providing home care only, is planning to build an inpatient facility with six beds.) The range of maximum patient load among the 16 hospice programs reporting this information is from 21 to 30; one hospice indicated there would be no limit. The average length of care reported by 15 programs ranged from less than seven days to more than 36 days.

Among those hospices providing information about the cost of their services, one reported a total cost of $800 for an average of 50 days. Table 5 shows the responses of five additional hospices.

The Wall Street Journal of March 27, 1978, reported that the New Haven, Connecticut, Hospice found that an average patient was cared for at home for about three months and required 15 visits from physicians and nurses at a total cost

TABLE 2.—*California Counties with Hospices in Planning or Organizational Stages (As of March 1978)*

Contra Costa (2)	San Francisco
Fresno	San Luis Obispo
Humboldt	San Mateo
Los Angeles (3)	Tulare

TABLE 3.—*Starting Year of Operational Hospice Programs*

Year	*Number*	*Year*	*Number*
1974	1	1977	9
1975	..	1978	2
1976	4		—
		Total	16

TABLE 4.—*Sponsorship of Operational Hospice Programs*

Community	6
Hospital	4
Home Health Agency	3
Other	3
Prepaid Group Practice Plan (1)	
Health Professionals (2)	

TABLE 1.—*Operational Hospice Programs in California*

County	*City*	*Hospice*
Alameda	Hayward	Kaiser Hayward Hospice Pilot Project
Los Angeles	Canoga Park	Hospice at Parkwood; Parkwood Community Hospital
	Torrance	Hospital/Home Health Care Agency
	Van Nuys	Continuity of Life Program; National In-Home Health Services
Marin	Kentfield	Hospice of Marin
Monterey	Carmel	Hospice of the Monterey Peninsula
Orange	Laguna Hills	Hospice Orange County, Inc.
San Diego	El Cajon	Acute Care Hospice Unit, El Cajon Valley Hospital
	San Diego	Expanded Patient Care-Hospice Program; College Park Hospital
	San Diego	San Diego County Hospice Corporation
Santa Barbara	Santa Barbara	Hospice of Santa Barbara County, Inc.
Santa Clara	Palo Alto	Midpeninsula Health Service, Inc.
Solano	Vallejo	Hospice Services of Solano
Sonoma	Santa Rosa	Home Hospice of Sonoma County
Ventura	Oxnard	Mercy Hospice of St. John's Hospital
	Thousand Oaks	Canejo Hospice, Inc.

TABLE 5.—*Cost Per Hospice Day/Visit*

Hospice	*Cost Per Day*	*Cost Per Visit*	*Average Number of Days*
1	$	$30-31	46
2	....	32	14
3	50-60	....	20
4	200	....	7
5	110	....	13

of about $450.[1] An article by Longo and Darr in *Hospital Progress*[2] reports a cost of $100 to $110 per day of inpatient care at the New Haven Hospice. It is apparent that the lack of precise information is due, in part, to lack of uniform accounting procedures or the insufficient experience of recently-formed hospices.

Information from 14 programs showed that approximately 1,200 terminally ill patients had been served by the hospice programs in California by the end of February 1978. The median age of these patients was 63. The total number of beds provided for terminally ill patients by four hospice programs with inpatient facilities was 52. Only one of the 15 programs that responded to the survey question stated that it has not conducted a public information program about hospices.

Of 15 programs responding, eight have Medical Advisory Committees, two have what they call either professional or health care advisory committees and five have neither. Of 16 which responded, ten have boards of directors (two of those are the boards of their hospitals), and five have none. Of the 15 hospices providing information about their staff, eight have medical directors, although most of the others have physicians who serve as part-time volunteer counselors to their programs.

The foregoing provides an overview of the status and some characteristics of the hospice movement in California. Judging from the publicity such programs have received, there would appear to be little doubt that hospices will find a ready place and occupy their own niche within the health care system; rarely has such an activity taken place which captured the interest and involvement of so many segments of the community. If any ingredient appears to be lacking at this early stage, it is that of attracting and involving minority and low income people. This represents a current weakness to the full-scale development of a concept and program which has the potential of revolutionizing an important aspect of the caring function.

A problem of deep concern to the hospice movement is that of securing reimbursement for the services they provide. At the time of this survey, grants from public and private sources were supporting several of them. Contributions in kind and in money from community resources were enabling most to function. A handful were managing to cover costs of specific services by reimbursement from certain insurance programs, as well as from Medicare and Medicaid (Medi-Cal).

There can be no doubt that with the eventual institution of accreditation procedures, aided by changes in legislation and insurance programs, more formal methods of reimbursement will enable hospices to become more self-sustaining. Their greatest strength lies in the concept they promote, in the appeal they will have to the public and, above all, in the humanistic approaches they employ in the care of terminally ill patients.

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Refer to: Brodsky JB: Epidural blood patch—A safe, effective treatment for postlumbar-puncture headaches (Medical Information). West J Med 129:85-87, Jul 1978

Medical Information

Epidural Blood Patch

A Safe, Effective Treatment for Postlumbar-Puncture Headaches

JAY B. BRODSKY, MD
Stanford, California

CORNING DESCRIBED the first postlumbar-puncture headache (PLPH) in 1885.[1] Since then, many different treatments have been advocated for this common, iatrogenic complication of diagnostic, therapeutic and anesthetic lumbar punctures.[2] Bed rest, increased fluid intake and analgesic drugs constitute the basic management for patients with PLPH. Since 1970 anesthesiologists have used the epidural blood patch (EBP) to treat severe PLPH. The purpose of this review is to familiarize other physicians carrying out lumbar punctures with the effectiveness and safety of the epidural blood patch procedure.

Bier in 1898, Sicard in 1902 and MacRobert in 1918 postulated that PLPH was due to leakage of spinal fluid through the dural puncture site.[1] Support for this theory came from manometric studies which showed a significant decrease in spinal fluid pressure between the time of spinal puncture and the onset of PLPH.[3,4] Direct observations during myeloscopy,[5] during surgical operation[6] and at autopsy[4] confirm that the dural hole remains patent and continues to leak fluid in patients with PLPH. Headaches identical with PLPH were produced acutely by draining spinal fluid from healthy human subjects.[7]

When a patient with PLPH assumes an upright position, the relative deficit in spinal fluid volume presumably deprives the brain of its fluid cushion and places tension on pain sensitive anchoring structures. Thus classically, the headache appears or is exacerbated by standing and is relieved by lying down. The headaches, which vary in intensity, usually occur one to three days following lumbar puncture and may be associated with nausea, vomiting, dizziness or visual disturbances. The mean duration of untreated PLPH is four days,[8] and 80 percent of patients will recover spontaneously within two weeks.[9] However, rarely, PLPH may persist for three to five months.[6,10]

Since PLPH is believed to be caused by fluid leak, a variety of attempts have been made to seal the dural rent in order to relieve the headache. Nelson[4] in 1930 used catgut dural plugs and successfully alleviated PLPH in approximately 50 percent of his patients. However, technical difficulty with this method, and a 50 percent incidence of cauda equina syndrome following its use, prevented the widespread acceptance of this technique. Nelson theorized that epidural bleeding from a traumatic dural puncture might lead to clot formation over the dural tear, which, in turn, would prevent spinal fluid loss. Gormley stated that the incidence of PLPH was lower than anticipated after inadvertent bloody spinal taps.[11] He reported the cases of seven patients, in all of which there was immediate relief of PLPH when 2 to 3 ml of autologous venous blood was injected into the patients' lumbar epidural spaces.[11] Ozdil claimed a 100 percent success rate in preventing PLPH in surgical patients undergoing spinal anesthesia by depositing 2.5 ml of clotted autologous blood epidurally as the spinal needle was being withdrawn.[12] DiGiovanni popularized the technique now known as epidural blood patching (EBP) for the treatment of PLPH.[13,14]

To carry out a epidural blood patch the patient is placed in the lateral decubitus position and the back is prepped and draped. A skin wheal is raised using a local anesthetic, and a needle is placed in the epidural space at the same level as the previous spinal puncture. Using aseptic technique, a venipuncture is done and 5 to 10 ml of blood is withdrawn with a plastic syringe and then injected into the epidural space. The patient is kept supine for 30 to 60 minutes and liberal amounts of fluids are given intravenously. The therapeutic results of EBP are dramatic. The patient usually notes total relief of symptoms on first assuming the upright position. Headaches seldom recur. Since Gormley's[11] and DiGiovanni's[13,14] initial reports, thousands of epidural blood

From the Department of Anesthesia, Stanford University School of Medicine.

Submitted November 23, 1977.

Reprint requests to: Jay B. Brodsky, MD, Department of Anesthesia, S276, Stanford University Medical Center, Stanford, CA 94305.

TABLE 1.—*Published Results of Epidural Blood Patch (EBP) for the Treatment of Postlumbar-Puncture Headaches (PLPH)*

Source	*Year*	*Number Patients*	*Relief After First EBP*	*Relief After Second EBP*	*No Relief*
Gormley[11]	1960	7	7 (100.0%)	....	0
DiGiovanni[13]	1970	45	41 (91.1%)	....	4 (8.9%)
DiGiovanni[14]	1972	63	61 (96.8%)	....	2 (3.2%)
Glass[15]	1972	50	47 (94.0%)	....	3 (6.0%)
DuPont[16]	1972	42	40 (95.2%)	1/1	1 (2.4%)
Vondrell[17]	1973	60	58 (96.7%)	....	2 (3.3%)
Ostheimer[18]	1974	185	182 (98.4%)	....	3 (1.6%)
Abouleish[19]	1975	118	105 (89.0%)	10/11	3 (2.5%)
TOTALS		570	541 (94.9%)		18 (3.2%)

patches have been done and many clinical studies have substantiated the effectiveness of treating PLPH with EBP[15-19] (See Table 1). Ninety-five percent of headaches are relieved with a single EBP, and an overall cure rate of 97 percent is achieved if a second blood patch is administered.

The epidural blood patch probably forms a gelatinous tamponade which prevents further leakage of spinal fluid allowing the dura to undergo normal healing.[14] Placement of unclotted autologous blood in the epidural space results in no greater tissue reaction than that which occurs following routine lumbar puncture, and less than that following laminectomy.[14] Large volumes of saline deposited in the epidural space will relieve PLPH,[20,21] but saline is readily absorbed and consequently the relief produced may only be temporary.[22,23] Epidural blood patching effects a permanent cure for the headache. Unfortunately, for unknown reasons, prophylactic placement of unclotted autologous blood epidurally at the time of lumbar puncture will not prevent PLPH.[23] Regional anesthesia can be carried out without difficulty at a later date at the same lumbar level as the epidural blood patch.[24]

A few patients have complaint of transient paresthesias in their legs and toes, stiff neck, abdominal cramping, tinnitus, vertigo or dizziness during the blood injection. An increase in temperature lasting several hours has been observed in some patients.[19] Mild backache at the puncture site, occasionally lasting as long as 48 hours, may occur.[18,19] No permanent neurologic complications have been reported following EBP.[19] A very small number of patients in whom this procedure is done may have uncomfortable neurologic symptoms. In two cases, patients had severe radicular leg pains following successful treatment of PLPH with epidural injection of 10 ml and 7.5 ml of autologous blood.[25,26] The clot from too large a volume of injected blood may have caused nerve root compression.[25] DiGiovanni,[25] in his discussion of the first case, felt that the radicular pain symptoms were secondary to hematoma formation from traumatic epidural needle placement, and were unrelated to the volume of blood actually injected. It would seem prudent, however, to use smaller volumes of blood in older and shorter patients.[25] This may also be true in pregnant patients where the epidural space is decreased in size; but, experience with the epidural blood patch during pregnancy is unreported.

Two complications feared after epidural blood patch are epidural abscess formation[27] and adhesive arachnoiditis. Neither has yet been reported to follow EBP, and the latter is more theoretical than a real consideration.[14] Patients with septicemia, local infection or inflammation in the lumbar back area, patients with blood dyscrasias and those receiving anticoagulant therapy should not receive EBP.[14,20] If bleeding occurs during the EBP the procedure should be discontinued, since subsequent hematoma formation may cover the dural hole, and the addition of the EBP may lead to nerve root compression.[25] If the headache persists, the epidural blood patch may be reattempted the following day at a different interspace.[20]

The reported incidence of PLPH following spinal anesthesia in general is 13 percent, and in obstetrics is 18 percent. PLPH occurs in 32 percent of patients after diagnostic lumbar punctures. Although the use of small gauge needles for lumbar puncture has decreased the overall occurence,[28,29] PLPH still is common. If PLPH is refractory to conservative management, or if the hospital stay is prolonged because of the headache and associated symptoms, autologous epidural

blood patching should be considered. The remarkably high success rate of this procedure, coupled with its extremely low morbidity, makes epidural blood patching a safe, sure method for treating post-lumbar puncture headaches.

Summary

Postlumbar-puncture headache is believed to result from continued leakage of spinal fluid through the dural perforation. PLPH can be treated with bed rest, increased fluid intake and analgesic drugs. An epidural blood patch should be considered for PLPH refractory to conservative management. Placement of 5 to 10 ml of autologous blood in the epidural space will seal the dural puncture site and relieve the headache and associated symptoms. The remarkably high success rate of this simple procedure, coupled with an extremely low morbidity, makes epidural blood patching a safe and effective method for treating PLPH.

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in memoriam

Ahnlund, Nels W., San Jose. Died January 12, 1978, aged 62. Graduate of the University of Minnesota Medical School, Minneapolis, 1940. Licensed in California in 1940. Dr. Ahnlund was a member of the Santa Clara County Medical Society.

Carson, Merl J., Orange. Died April 26, 1978, aged 64. Graduate of Vanderbilt University School of Medicine, Nashville, 1938. Licensed in California in 1950. Dr. Carson was a member of the Orange County Medical Association.

Cron, Heinz E., San Francisco. Died April 25, 1978 in Ross, aged 64. Graduate of Washington University School of Medicine, St. Louis, 1939. Licensed in California in 1948. Dr. Cron was a member of the San Francisco Medical Society.

Dobson, Leonard G., San Francisco. Died April 12, 1978 in Menlo Park, aged 74. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1929. Licensed in California in 1931. Dr. Dobson was a member of the San Francisco Medical Society.

Feinstein, Bertram, San Francisco. Died April 15, 1978 in San Francisco of cancer, aged 64. Graduate of the University of Manitoba Faculty of Medicine, Winnipeg, 1938. Licensed in California in 1948. Dr. Feinstein was a member of the San Francisco Medical Society.

Hauser, Roger G., Tustin. Died September 27, 1977 of histiocytic lymphoma, aged 46. Graduate of the University of Southern California School of Medicine, Los Angeles, 1957. Licensed in California in 1958. Dr. Hauser was a member of the Orange County Medical Association.

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King, Marion R., Napa. Died April 15, 1978 in Napa, aged 88. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1917. Licensed in California in 1917. Dr. King was a retired member of the Solano County Medical Society.

Maguire, Vincent Joseph, Hayward. Died May 12, 1978, aged 35. Graduate of Tufts University School of Medicine, Boston, 1968. Licensed in California in 1969. Dr. Maguire was a member of the Alameda-Contra Costa Medical Association.

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Talbot, David R., Camarillo. Died March 25, 1978 in Wailuka on Maui, Hawaii, aged 82. Graduate of Western Reserve University School of Medicine, Cleveland, 1921. Licensed in California in 1953. Dr. Talbot was a member of the Ventura County Medical Society.

Tuta, Joseph A., Long Beach. Died April 9, 1978, aged 77. Graduate of Rush Medical College, Chicago, 1929. Licensed in California in 1943. Dr. Tuta was a member of the Los Angeles County Medical Association.

Weisman, Samuel A., Los Angeles. Died September 2, 1977 in Los Angeles of heart disease, aged 86. Graduate of the University of Minnesota Medical School, Minneapolis, 1918. Licensed in California in 1941. Dr. Weisman was a member of the Los Angeles County Medical Association.

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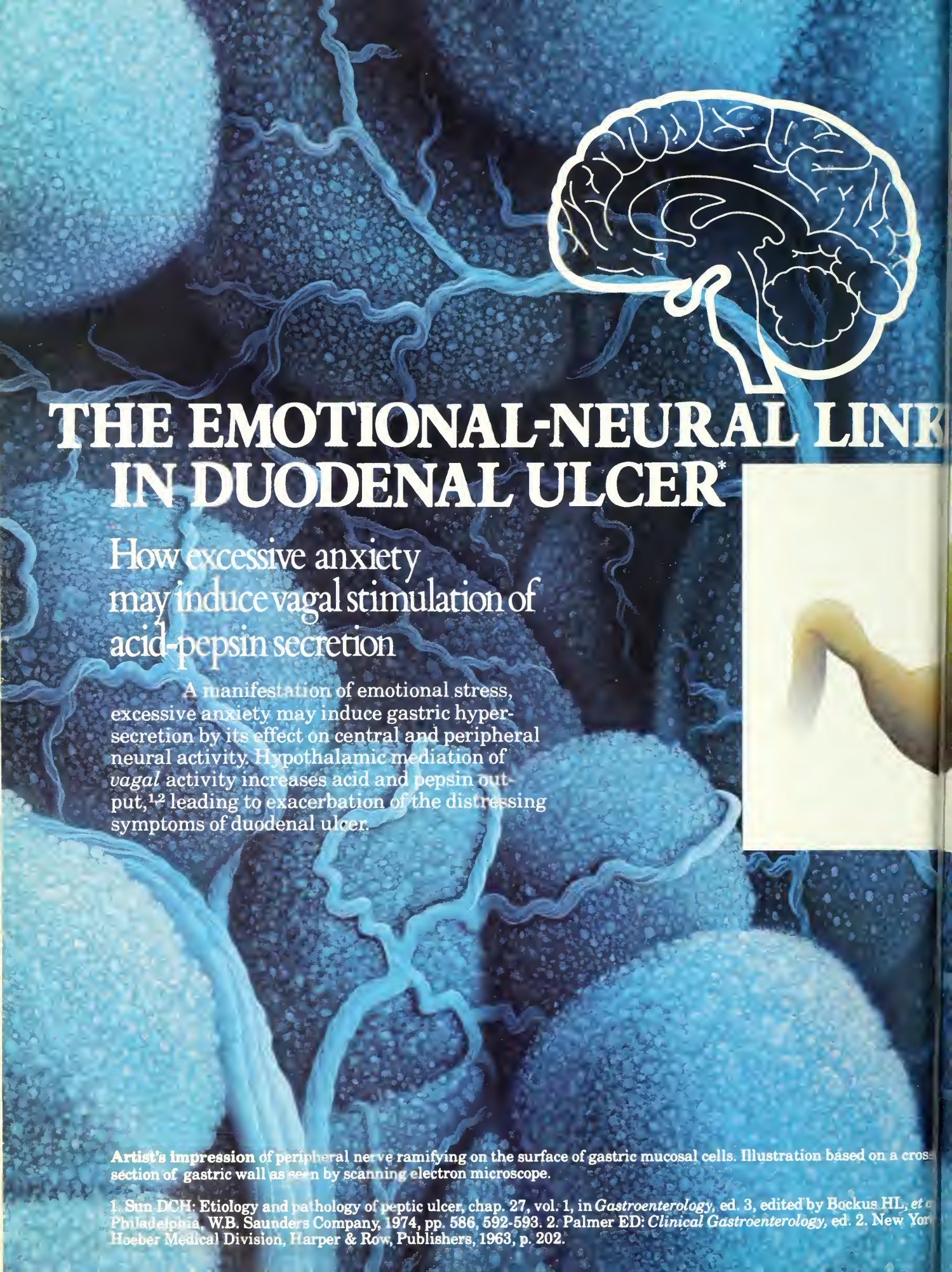

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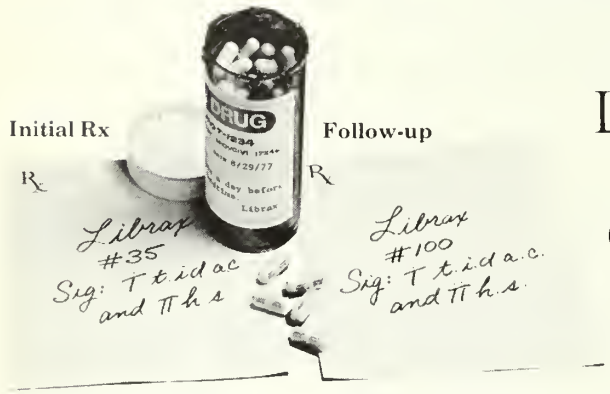

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BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

AID™—The Antibiotics Indications Device—Developed by Exerpta Medica Services, Inc., Editorial Consultant Committee (Chairman: Maxwell Finland, MD, Professor of Medicine, Harvard University). Excerpta Medica Services, Inc., P.O. Box 3085, Princeton, NJ (08540), 1978. 32-page booklet, plus device in back-cover pocket; 3 or less, $11.95 each; 4 to 10, $10.75 each; 11 to 25, $10.25 each; quantity discount prices upon request.

BASIC & CLINICAL IMMUNOLOGY—Second Edition—Edited by H. Hugh Fudenberg, MD, Protessor and Chairman, Department of Basic and Clinical Immunology and Microbiology, Medical University ot South Carolina, Charleston; Daniel P. Stites, MD, Associate Professor of Laboratory Medicine and Medicine, Director, Immunology Laboratory, University of Calitornia, San Francisco; Joseph L. Caldwell, MD, Assistant Professor of Medicine, University of California, San Francisco, and Veterans Administration Hospital, San Francisco; and J. Vivian Wells, MD, FRACP, FRCPA, Senior Staff Specialist in Clinical Immunology, Kolling Institute of Medical Research, Royal North Shore Hospital, Sydney. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1978. 758 pages, $14.50.

BETTER HEALTH THROUGH NUTRITION—A Guide for Cancer Patients—Harry Drasin, MD, Oncology Fellow, Claire Zellerbach Saroni Tumor Institute, Mt. Zion Hospital and Medical Center, San Francisco, American Cancer Society Clinical Fellow; Ernest Rosenbaum, MD, Associate Chief of Medicine, Mt. Zion Hospital and Medical Center; Medical Director, San Francisco Regional Cancer Foundation; Carol A. Stitt, RD, Therapeutic Dietician, Mt. Zion Hospital and Medical Center; and Isadora R. Rosenbaum, Medical Assistant, San Francisco. Copies are available from The Gift Shop, Mt. Zion Hospital and Medical Center, P.O. Box 7921, San Francisco, CA (94120), 1978. 59 pages, $2.00.

CARDIAC CATHETERIZATION AND ANGIOCARDIOGRAPHY—Third Edition—David Verel, MA, MD, FRCP, Consultant Cardiologist to Sheffield Area Health Authority (Teaching); Lecturer in Cardiology in the University of Sheffield; Ronald G. Grainger, MD, FRCP, DMRD, FRCR, FACR(Hon), Northern General Hospital, Sheffield, Consultant Radiologist to Sheffield Area Health Authority (Teaching), Clinical Teacher in Radiodiagnosis in the University of Sheffield, Visiting Professor, Radiology Dept., Stanford University, Palo Alto, CA; With a chapter on echocardiography by D. R. Naik, MB, ChB, DMRD, FRCR, Consultant Radiologist to Sheffield Area Health Authority (Teaching), Clinical Teacher in Radiodiagnosis in the University of Sheffield; Foreword by Sir John McMichael, MD, FRCP, FRS, Sometime Director, Postgraduate Medical Federation, London, Sometime Professor of Medicine, Royal Postgraduate Medical School, London. Churchill Livingstone—Medical Division, Longman Inc., 19 West 44th St., New York City (10036), 1978. 239 pages, $29.50.

DAVIDSON'S PRINCIPLES AND PRACTICE OF MEDICINE—A Textbook for Students and Doctors—Twelfth Edition—Edited by John Macleod, MB, ChB, FRCPEdin, Head of University Department of Medicine, Western General Hospital; Consultant Physician, Western General Hospital, Royal Edinburgh Hospital and Clinic for Rheumatic Diseases, Royal Intirmary, Edinburgh. Churchill Livingstone—Medical Division, Longman Inc., 19 West 44th St., New York Clty (10036), 1977. 978 pages, $16.00 (softbound).

ENERGETICS—Clarence M. Agress, MD. Grosset & Dunlap, Publishers, 51 Madison Ave., New York, NY (10010), 1978. 166 pages, $10.00, $11.50 in Canada.

EVANS' HISTOLOGICAL APPEARANCES OF TUMORS—Third Edition: Volumes I and II—David J. B. Ashley, TD, MD, FRCPath, Consultant Pathologist, Morriston Hospital, Swansea; Visiting Professor of Pathology, University of Chicago; Visiting Scholar, State University of New York, Downstate Medical Center; Formerly Research Fellow, Armed Forces Institute of Pathology, Washington, DC; Senior Registrar in Pathology, David Lewis Northern Hospital, Liverpool. Churchill Livingstone—Medical Division, Longman Inc., 19 West 44th St., New York City (10036), 1978. 858 pages, in 2 volumes, $85.00.

HEALTH CARE CAPITAL: COMPETITION AND CONTROL—Proceedings of Capital Investment Conterence Sponsored by the University ot Pittsburgh Graduate School ot Public Health and Supported under Federal Contract No. HRA 230-75-0208. Editors: Gordon K. MacLeod, Professor and Chairman, Dept. of Health Services Administration, Graduate School ot Public Health, University ot Pittsburgh; and Mark Perlman, The University Professor of Economics, University of Pittsburgh. Ballinger Publishing Company, 17 Dunster Street, Cambridge, MA (02138), 1978. 411 pages, $22.50.

THE HOSPICE MOVEMENT—A Better Way ot Caring for the Dying—Sandol Stoddard. Stein and Day Publishers, Scarborough House, Briarcliff Manor, NY (10510), 1978. 266 pages, $8.95.

THE MALPRACTITIONERS—John Guinther. Anchor Press/Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1978. 347 pages, $10.00.

POVERTY AND HEALTH—Economic Causes and Consequences of Health Problems—Harold S. Lutt, PhD, Assistant Protessor of Health Economics in the Health Services Research Program, Stanford University School of Medicine, Stanford, Calitornia. Ballinger Publishing Company, 17 Dunster Street, Harvard Square, Cambridge, MA (02138), 1978. 263 pages, $16.50.

Brief Summary of Prescribing Information
Combined TEGOPEN® (cloxacillin sodium)
Capsules and Oral Solution
For complete information, consult Official Package Circular. (12) TEGOPEN 9/11/75
Indications: Although the principal indication for cloxacillin sodium is in the treatment of infections due to penicillinase-producing staphylococci, it may be used to initiate therapy in such patients in whom a staphylococcal infection is suspected. (See Important Note below.)
Bacteriologic studies to determine the causative organisms and their sensitivity to cloxacillin sodium should be performed.
Important Note: When it is judged necessary that treatment be initiated before definitive culture and sensitivity results are known, the choice of cloxacillin sodium should take into consideration the fact that it has been shown to be effective only in the treatment of infections caused by pneumococci, Group A beta-hemolytic streptococci, and penicillin G-resistant and penicillin G-sensitive staphylococci. If the bacteriology report later indicates the infection is due to an organism other than a penicillin G-resistant staphylococcus sensitive to cloxacillin sodium, the physician is advised to continue therapy with a drug other than cloxacillin sodium or any other penicillinase-resistant semi-synthetic penicillin.
Recent studies have reported that the percentage of staphylococcal isolates resistant to penicillin G outside the hospital is increasing, approximating the high percentage of resistant staphylococcal isolates found in the hospital. For this reason, it is recommended that a penicillinase-resistant penicillin be used as initial therapy for any suspected staphylococcal infection until culture and sensitivity results are known.
Cloxacillin sodium is a compound that acts through a mechanism similar to that of methicillin against penicillin G-resistant staphylococci. Strains of staphylococci resistant to methicillin have existed in nature and it is known that the number of these strains reported has been increasing. Such strains of staphylococci have been capable of producing serious disease, in some instances resulting in fatality. Because of this, there is concern that widespread use of the penicillinase-resistant penicillins may result in the appearance of an increasing number of staphylococcal strains which are resistant to these penicillins.
Methicillin-resistant strains are almost always resistant to all other penicillinase-resistant penicillins (cross-resistance with cephalosporin derivatives also occurs frequently). Resistance to any penicillinase-resistant penicillin should be interpreted as evidence of clinical resistance to all, in spite of the fact that minor variations in *in vitro* sensitivity may be encountered when more than one penicillinase-resistant penicillin is tested against the same strain of staphylococcus.
Contraindications: A history of a previous hypersensitivity reaction to any of the penicillins is a contraindication.
Warning: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.
There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents, e.g., pressor amines, antihistamines, and corticosteroids.
Safety for use in pregnancy has not been established.
Precautions: The possibility of the occurrence of superinfections with mycotic organisms or other pathogens should be kept in mind when using this compound, as with other antibiotics. If superinfection occurs during therapy, appropriate measures should be taken.
As with any potent drug, periodic assessment of organ system function, including renal, hepatic, and hematopoietic, should be made during long-term therapy.
Adverse Reactions: Gastrointestinal disturbances, such as nausea, epigastric discomfort, flatulence, and loose stools, have been noted by some patients. Mildly elevated SGOT levels (less than 100 units) have been reported in a few patients for whom pretherapeutic determinations were not made. Skin rashes and allergic symptoms, including wheezing and sneezing, have occasionally been encountered. Eosinophilia, with or without overt allergic manifestations, has been noted in some patients during therapy.
Usual Dosage: Adults: 250 mg. q.6h.
Children: 50 mg./Kg./day in equally divided doses q.6h. Children weighing more than 20 Kg. should be given the adult dose. Administer on empty stomach for maximum absorption.
N.B.: INFECTIONS CAUSED BY GROUP A BETA-HEMOLYTIC STREPTOCOCCI SHOULD BE TREATED FOR AT LEAST 10 DAYS TO HELP PREVENT THE OCCURRENCE OF ACUTE RHEUMATIC FEVER OR ACUTE GLOMERULONEPHRITIS.
Supplied: Capsules—250 mg. in bottles of 100, 500 mg. in bottles of 100. Oral Solution—125 mg./5 ml. in 100 ml. and 200 ml. bottles.

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*resistance to penicillin G among community-acquired staph infections. Data on file, Bristol Laboratories.

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(cloxacillin sodium)

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- Effective against nonpenicillinase-producing staphylococci, beta-hemolytic streptococci, and pneumococci.†

†NOTE: The choice of Tegopen should take into consideration the fact that it has been shown to be effective only in the treatment of infections caused by pneumococci, Group A beta-hemolytic streptococci, and penicillin G-resistant and penicillin G-sensitive staphylococci. If the bacteriology report later indicates that the infection is due to an organism other than a penicillin G-resistant staphylococcus sensitive to cloxacillin sodium, the physician is advised to continue therapy with a drug other than cloxacillin sodium or any other penicillinase-resistant semisynthetic penicillin. The clinical significance of *in vitro* data is unknown.

- 10 times more active against strep than staph.
- Well absorbed from the G.I. tract.‡

‡Maximum absorption occurs when Tegopen is taken on an empty stomach, preferably 1-2 hrs. before meals.

Please see brief summary for prescribing information.

Personally, Steve could never speak up for milk.

In TV commercials, you'll often see people speaking up for milk. Steve Allen and his wife Jayne Meadows are also seen on TV telling viewers about Mocha Mix... 100% milk free!

Matter of fact, this non-dairy creamer would have been found in their home way before they ever filmed the Mocha Mix series of commercials. Steve is allergic to milk products. Yet, he likes the splash of luxury and fresh taste in his coffee, on cereal, fruit and dessert, even in cooking. For the Allen household, Mocha Mix is the perfect answer.

It could well be the answer for many people who rely on you for their dietary needs, those with an allergy similar to Steve's, or a lactose intolerance. And, for many who must maintain a fat-restricted diet you should know that Mocha Mix is one non-dairy creamer that contains no coconut oil, giving it the highest ratio of unsaturated to saturated fat of any creamer. It easily exceeds the accepted standard 2:1 ratio. It's 100% cholesterol free, too. No wonder Mocha Mix is not just another non-dairy creamer, but the one you can rely on most for your patients who can't speak for milk, either.

NUTRITION INFORMATION

Portion Size 1 Fluid Ounce (2 Tbs.)

Servings Per Container	16
Calories	40
Protein	0 grams
Carbohydrate	3 grams
Fat	3 grams
Percent of Calories from Fat	73%
Polyunsaturated Fat	1 gram
Saturated Fat	0 grams
Cholesterol (Δ) (0 mg/100g)	0 mg

In addition to the pint and quart size found in the dairy case of most grocery stores, Mocha Mix is available in 4 ounce and ½ oz. portion packs for hospitals and institutions.

Interested? Send us a note and we will send you a supply of coupons your patients can redeem at their grocers. Hospital service may also be supplied upon request. Mail to: Mocha Mix Dept. Presto Food Products, Inc. P.O. Box No. 21908, Los Angeles, Calif. 90021

Percentage of U.S. Recommended Daily Allowance (U.S. RDA)*

*Contains less than 2% of the U.S. RDA of Protein, Vitamin A, Vitamin C, Thiamine, Riboflavin, Niacin, Calcium, Iron.

ΔInformation on fat and cholesterol content is provided for individuals who, on the advice of a physician, are modifying their total dietary intake of fat and cholesterol.

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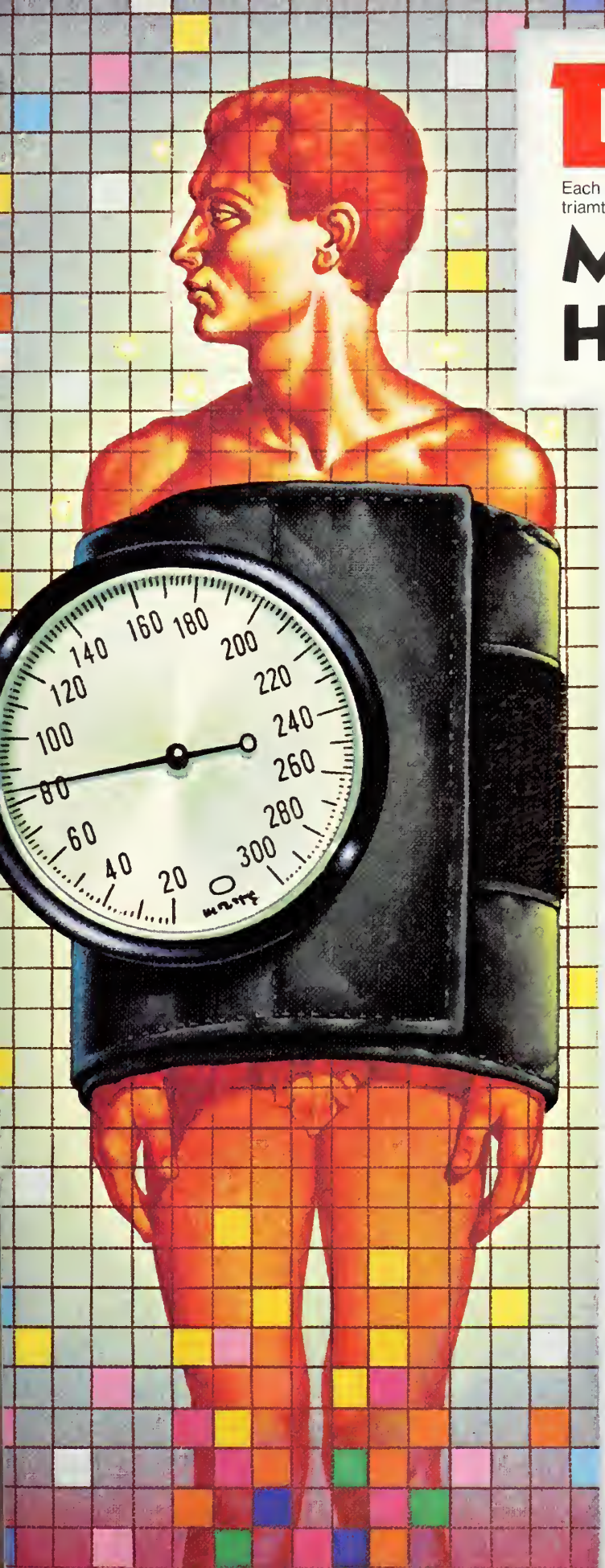

Dyazide®

Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

Makes Sense in Hypertension*

Before prescribing, see complete prescribing information in SK&F Co. literature or *PDR*. A brief summary follows:

* **Warning**
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K+ frequently; both can cause K+ retention and elevated serum K+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

Supplied: Bottles of 100 and 1000 capsules; Single Unit Packages of 100 (intended for institutional use only).

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Tablets

Percodan® Ⓒ II

DESCRIPTION Each yellow, scored tablet contains 4.50 mg oxycodone HCl (WARNING: May be habit forming), 0.38 mg oxycodone terephthalate (WARNING: May be habit forming), 224 mg. aspirin, 160 mg phenacetin, and 32 mg. caffeine.

INDICATIONS For the relief of moderate to moderately severe pain

CONTRAINDICATIONS Hypersensitivity to oxycodone, aspirin, phenacetin or caffeine.

WARNINGS Drug Dependence Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCODAN®, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, PERCODAN® is subject to the Federal Controlled Substances Act.

Usage in ambulatory patients Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCODAN® should be cautioned accordingly

Interaction with other central nervous system depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCODAN® may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in pregnancy Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, PERCODAN® should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children PERCODAN® should not be administered to children.

Salicylates should be used with caution in the presence of peptic ulcer or coagulation abnormalities.

PRECAUTIONS Head injury and increased intracranial pressure The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries

Acute abdominal conditions The administration of PERCODAN® or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients PERCODAN® should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture

Phenacetin has been reported to damage the kidneys when taken in excessive amounts for a long time.

ADVERSE REACTIONS The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation and pruritus.

DOSAGE AND ADMINISTRATION Dosage should be adjusted according to the severity of the pain and the response of the patient The usual adult dose is one tablet every 6 hours as needed for pain

DRUG INTERACTIONS The CNS depressant effects of PERCODAN® may be additive with that of other CNS depressants. See WARNINGS.

DEA Order Form Required.

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CONSIDERATIONS FOR ORAL NARCOTIC ANALGESIC USE:

1. Determine need

What is causing pain? How is it perceived by you and your patient?

2. Prescribe a rapid-acting agent

Select a readily-absorbed oral agent that usually acts within 15 to 30 minutes.

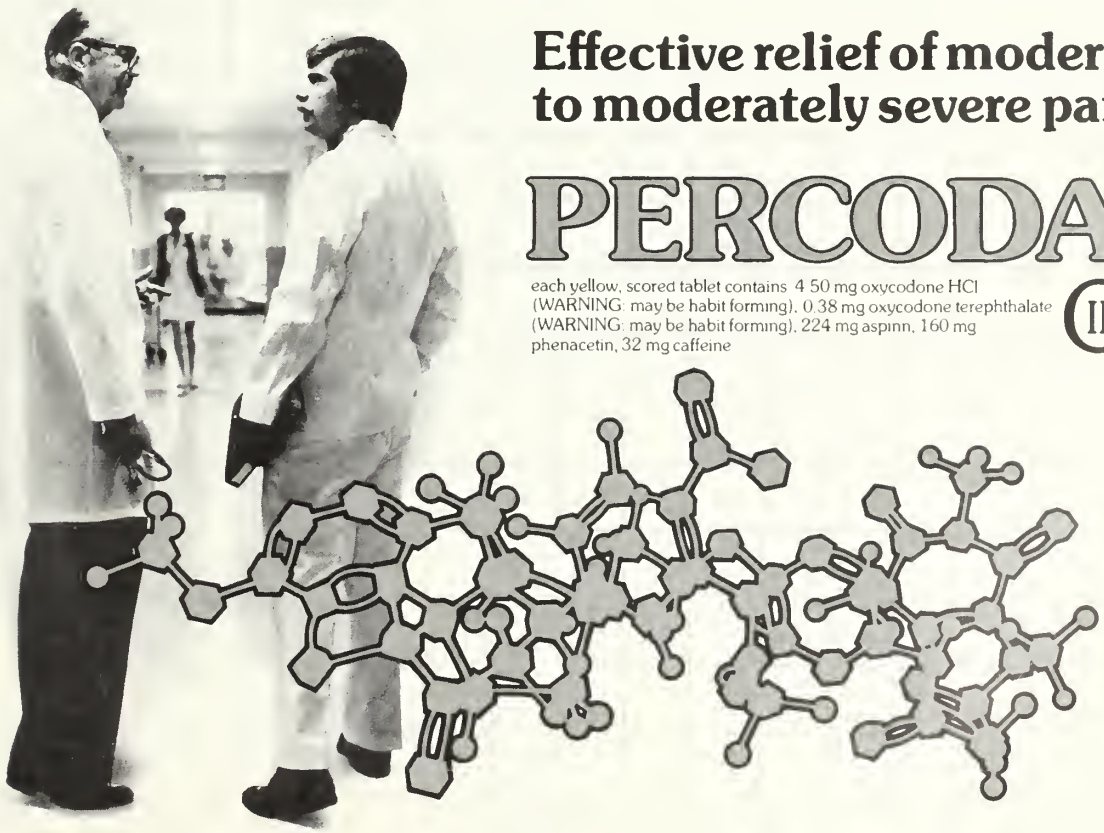
3. Minimize potential risk

Prescribe in limited quantities for selected patients.

Schedule II classification means no refills, no telephone Rx. Patients with persistent pain must return for your evaluation of analgesic needs.

4. Provide adequate analgesia with minimum doses

Consider PERCODAN® because patients rarely ask for increased dosage. PERCODAN® relief can last up to six hours–until time for next tablet.



Effective relief of moderate to moderately severe pain

Tablets

PERCODAN®

each yellow, scored tablet contains 4.50 mg oxycodone HCl (WARNING: may be habit forming), 0.38 mg oxycodone terephthalate (WARNING: may be habit forming), 224 mg aspirin, 160 mg phenacetin, 32 mg caffeine

CII

PERCODAN® is a registered trademark of Endo Inc.

Please see facing page for Brief Summary of prescribing information.

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Time is the test of all things.

1954
1978

BRIEF SUMMARY

Indications Oral potassium therapy for the prevention and treatment of hypokalemia which may occur secondary to diuretic or corticosteroid administration. May be used in the treatment of cardiac arrhythmias due to digitalis intoxication.

Contraindications: Severe renal impairment with oliguria or azotemia, untreated Addison's disease, adynamia episodica hereditaria, acute dehydration, heat cramps and hyperkalemia from any cause.

Precautions: Potassium intoxication by oral administration rarely occurs in patients with normal kidney function, however, potassium supplements must be administered with caution, since the amount of the deficiency or daily dosage is not accurately known. Frequent checks of the clinical status of the patient, and periodic ECG and/or serum potassium levels should be made. High serum concentrations of potassium ion may cause death through cardiac depression, arrhythmias or arrest. This drug should be used with caution in the presence of cardiac disease.

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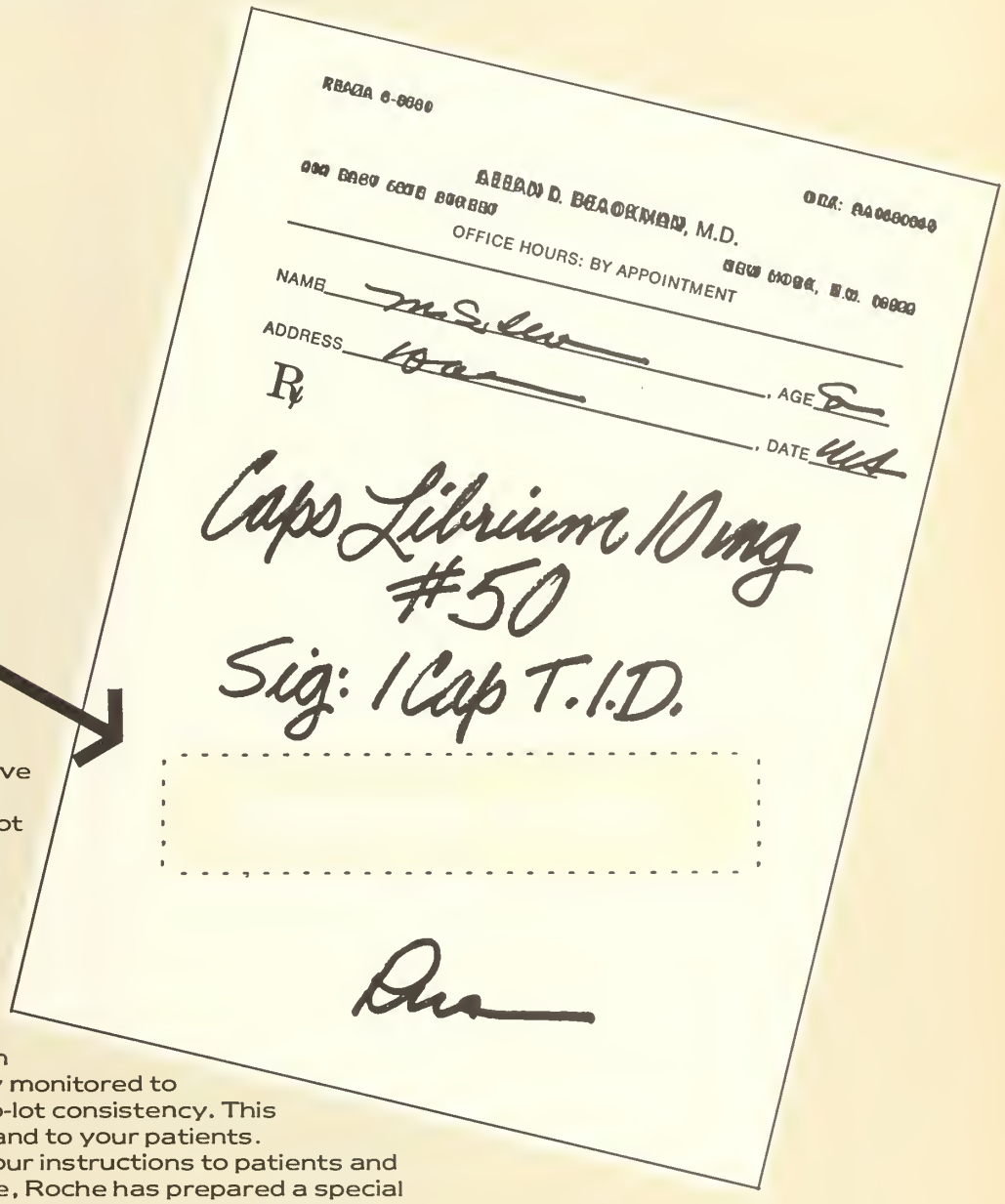

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Contraindications: Patients with known hypersensitivity to the drug.

Warnings: Warn patients that mental and/or physical abilities required for tasks such as driving or operating machinery may be impaired, as may be mental alertness in children, and that concomitant use with alcohol or CNS depressants may have an additive effect. Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported.

Usage in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (e.g., excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.

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Adverse Reactions: Theophylline may exert some stimulating effect on the central nervous system. Its administration may cause local irritation of the gastric mucosa, with possible gastric discomfort, nausea, and vomiting. The frequency of adverse reactions is related to the serum theophylline level and is not usually a problem at serum theophylline levels below 20 μg/ml.
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THE WESTERN
Journal of Medicine

Refer to: Toy PTCY, Schrier SL: Occlusive impedance plethysmography—A noninvasive method of diagnosis of proximal deep vein thrombosis. West J Med 129:89-93, Aug 1978

Occlusive Impedance Plethysmography

A Noninvasive Method of Diagnosis of Proximal Deep Vein Thrombosis

PEARL T. C. Y. TOY, MD, *and* STANLEY L. SCHRIER, MD, *Stanford, California*

The purpose of this study was to assess and confirm the accuracy of impedance plethysmography (IPG) by the occlusive cuff method, in detecting proximal (popliteal, femoral and iliac) deep vein thrombosis in patients with symptomatic limbs. In 27 patients 30 consecutive limbs were studied with concurrent venography and IPG. The IPG result was normal in 9 of 9 limbs which were normal on venography, and abnormal in 15 of 16 limbs which showed venographic evidence of proximal deep vein thrombosis (DVT). An abnormal IPG strongly suggests proximal DVT (predictive value 0.88). A normal IPG virtually rules out proximal DVT (predictive value 1.0).

THE PRESENCE of deep vein thrombosis (DVT) in the popliteal, femoral and iliac veins carries a high risk of pulmonary embolism.[1-3] At present, venography is the standard method of establishing the presence of deep vein thrombosis in the calf and thigh; however, it is far from ideal (Table 1). There are situations where venography is not feasible, and the procedure is not without risk. Perhaps the most serious consequence of its disadvantages is that physicians hesitate to order the test, and inaccurate clinical diagnoses are made. It has been repeatedly shown that clinical diagnosis of DVT is most unreliable.[8]

In the last several years, alternative methods have been developed that closely approximate the accuracy of venogrphy and, in addition, overcome some of its disadvantages. Of these, 125-I fibrinogen scanning provides accurate diagnosis of fresh calf vein thrombosis, while proximal thrombosis in the popliteal, femoral and iliac veins can be detected by impedance plethysmography.[9,10]

Impedance plethysmography or phlebography (IPG) was introduced and developed by Wheeler,[11] and in the last three years the occlusive cuff modification has been tested in several laboratories.[7,12,13] The accuracy of IPG has been variable, depending on details of the testing procedure, method of interpretation and the type of patient in whom the study is done. Accuracies of over 95 percent were achieved by Wheeler[11] and Hull[7,10] in the detection of symptomatic proximal deep vein thrombosis.

This method is based on considerations of venous physiology (Figure 1). Temporary occlusion of venous return by inflation of a thigh-cuff results in increase in venous volume of the calf;

From the Department of Medicine, Division of Hematology, Stanford University Hospital, Stanford.

Dr. Toy's research supported by Daland Fellowship for Research in Clinical Medicine, American Philosophical Society and the Dean's Fellowship of Stanford University.

Submitted November 3, 1977.

Reprint requests to: Stanley L. Schrier, MD, Department of Medicine, Division of Hematology, Stanford University School of Medicine, Stanford, CA 94305.

ABBREVIATIONS USED IN TEXT

DVT = deep vein thrombosis
IPG = impedance plethysmography (phlebography)

TABLE 1.—*Limitations of Ascending Contrast Venography*

Venography not feasible
Unstable patients in intensive care
Possible pregnancy
Veins inaccessible for dye injection
Iodine allergy
Complications
Pain
Thrombophlebitis[4]
Allergic reactions
Renal damage in patients with myeloma or pre-existing renal disease.[5]
Disadvantages
Expensive
Difficult to repeat to follow disease
Iliac vein thrombosis may not be detected.[6,7]
Physicians hesitate to order the test

release of the cuff results in a rapid decrease in calf volume as blood drains into the proximal veins. If thrombosis is present in the veins proximal to the calf, initial calf volume increase is diminished and, more important, the rate of outflow of blood from the calf is decreased. These changes in calf blood volume can be detected by measuring changes in electrical resistance (impedance) of the calf.

The purpose of this paper is to report our experience with the IPG in detecting symptomatic DVT, using concurrent venography as the standard.

Patients and Methods

Patients

All patients referred for venography in the four months between January 26 and May 31, 1977, were studied. These included both medical and surgical inpatients and outpatients. Although not excluded, no patient had overt cardiac failure and no patient had hip surgical operations. All patients referred had clinical symptoms or signs suggestive of deep vein thrombosis.

Venography

Ascending venography was done by the Stanford University Department of Radiology. The method of Rabinov and Paulin was used.[6]

Impedance Phlebography

A model 200 Impedance Plethysmograph (Cintor) was used according to the method of Wheeler.[11] The total rise and three second fall were measured and scored on a graph provided by H. B. Wheeler, MD (written communication, 1977) (Figure 2). The graph was developed by computer analysis of 390 IPG-venogram correlations.[14] A gray area divides the normal and abnormal areas.

Normal test results were those that fell on the upper gray border and above. Nondiagnostic test findings were those that fell on the lower gray border and in the gray area. Abnormal test results were those that fell below the lower gray border.

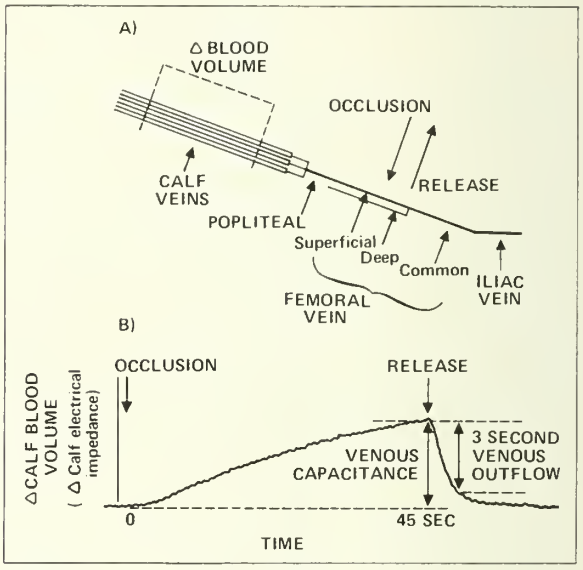

Figure 1.—Occlusive Impedance Phlebography (IPG). **A.** Schematic diagram of the deep veins of the lower extremities, **B.** IPG tracing showing calf blood volume changes following occlusion and release of a thigh tourniquet.

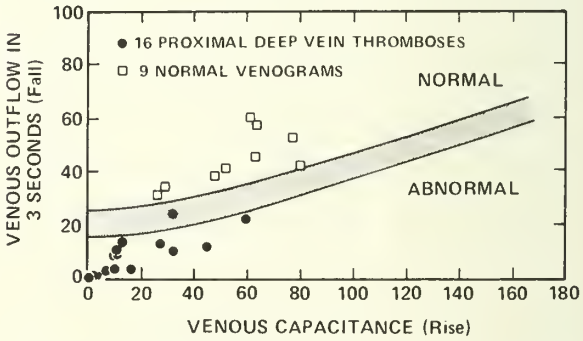

Figure 2.—Venous capacitance and 3-second outflow in 9 limbs with normal venograms and 16 limbs with thrombosis in the iliac, femoral or popliteal veins. (Graph provided by H. B. Wheeler, MD, Worcester, MA)

TABLE 2.—*Results of 30 IPG Venogram Correlations*

IPG	*Proximal DVT*	*Normal*	*Old DVT*	*Calf DVT*
Abnormal	15	0	1	1
Normal	0	9	0	2
Nondiagnostic	1	0	0	1
	16	9	1	4

DVT = deep vein thrombosis
IPG = impedance plethysmography

The most normal point of several measurements was used to represent the patient's IPG result.

If the initial result was abnormal, several maneuvers were tried before interpreting the test finding as abnormal: (1) If maximal filling during a 45 second cuff occlusion did not occur, a two-minute occlusion test run was done. (2) If the maximal filling was still small, the cuff was tightened. (3) If the outflow was slow, the cuff was loosened. (4) Different positions were tried. (5) Muscle relaxation was encouraged and medication given if the patient was in pain.

Venograms and IPG's were done and interpreted without knowledge of the result of the other, except in four patients, where the venogram result could have been inferred by person carrying out the IPG because it could be seen that the patients had been started on a regimen of heparin.

Results

Between January 26, 1977, and May 31, 1977, venograms were done on 36 limbs for clinically suspected deep vein thrombosis. Venograms were normal in 15 (42 percent) and showed thrombosis in the deep veins in 21 (52 percent).

All limbs were studied by IPG except for six patients who were immediately discharged when venograms were found to be negative. In the 30 IPG's that were compared with venography, 28 were done within 48 hours of venography and two within the subsequent two days. Table 2 summarizes the results of the 30 IPG-venogram correlations.

Proximal DVT

Table 2 shows that IPG correctly identified 15 out of 16 limbs with proximal DVT, defind as thrombosis in the iliac, femoral or popliteal vein. The sensitivity was then 94 percent. The test correctly identified nine out of nine normal limbs, a specificity of 100 percent. (For purposes of comparison, specificity is defined here, as in other series,[7,11] as number of test negatives/number of true negatives.)

In patients with less than two weeks of symptoms, 8/8 had abnormal IPG's. In those with symptoms longer than two weeks, 7/8 had abnormal IPG's.

Calf Vein DVT

Four limbs showed thrombosis of the calf veins only. IPG was abnormal in one patient, two had nondiagnostic IPG's and one was normal. There were two peroneal, two anterior tibial and two posterior tibial vein thrombi in four limbs.

Old DVT

One patient who had postphlebitic syndrome with ten years of chronic pain and swelling had an abnormal IPG. There were no acute symptoms. Venography showed evidence of old phlebitis with ragged vein walls, dilated superficial veins and nonvisualization of some deep veins.

The data were plotted on Wheeler's graph. If the graph of Hull and co-workers[7] was used, there was one false positive, but the overall accuracy remained 96 percent because the one nondiagnostic result would then be accurately diagnosed as abnormal.

Discussion

Overall accuracy of IPG in the detection of proximal deep vein thrombosis was 96 percent in this small series and agrees with the accuracy of 95 percent to 98 percent reported in the two largest series.[7,11] We have confirmed that impedance phlebography done and interpreted as described is a sensitive and specific test for the diagnosis of symptomatic deep vein thrombosis of the popliteal, femoral and iliac veins. It should be noted that the accuracy is reported to be lower in asymptomatic limbs, and in patients who have had surgical operations on the hip.[7]

Moser and associates[13] reported that the IPG detected only 61 percent of DVT. Of the subgroup that had thigh thrombosis, 76 percent (13/17) were detected by IPG. The sensitivity was still lower than that of this and other series.[7,11] The authors attributed this to the presence of collaterals in the four IPG negative patients. The difference could also be one of methodology. The

TABLE 3.—*Predictive Values of Impedance Plethysmography (IPG) in the Diagnosis of Proximal Deep Vein Thrombosis (DVT)*

	IPG	
	Abnormal	*Normal*
Proximal DVT (popliteal, femoral, iliac vein thrombi)	15	0
No proximal DVT (calf thrombi, no thrombi)	2	11
	17	11

Predictive value of abnormal IPG for proximal DVT: 15/17=0.88
Predictive value of normal IPG for no proximal DVT: 11/11=1.0

cuff pressure used and the method of analysis were different from that used in the present and other series.[7,11]

Test Interpretation

Positive IPG

As shown in Table 3, a properly carried out positive IPG with the patient relaxed is strong evidence for proximal DVT (predictive value 0.88). False positive rates (IPG abnormal/venogram normal) ranged from 1 percent to 4 percent in the largest series,[7,10,11] and were due to leg muscle tension, overt cardiac failure or pelvic tumor. In some institutions where there has been extensive experience with IPG, administration of heparin is started on the basis of a positive IPG result without venographic confirmation, provided there are no conditions that might result in a false positive test result.

Negative IPG

The false-negative rate (IPG normal/venogram abnormal) for proximal thrombosis is low in clinically abnormal limbs. None was missed in the present group (0/16) and only 1.7 percent (1/60) was missed in the larger series of Hull and associates.[10] A negative IPG result in a symptomatic leg then virtually rules out proximal deep vein thrombosis. The IPG, however, does not reliably detect small calf thrombi.[7,10,11] Symptomatic limbs with negative IPG results harbored 18 percent (2/11) and 16 percent (21/130) calf thrombi, respectively, in the present series and that of Hull and co-workers.[10]

The question then turns on the clinical significance of calf vein thrombi. When the thrombi are localized to the calf, the study of Kakkar suggests they rarely give rise to clinically significant pulmonary emboli; of 31 untreated calf thrombi in postoperative patients, none gave rise to clinically symptomatic pulmonary embolism.[1] Recently, studies on a small group of postoperative patients suggest that thrombi limited to the calf may give rise to pulmonary emboli. However, these emboli were small and clinically silent.[15] The major clinical importance of calf thrombosis then is the potential to propagate proximally. Many studies have shown that approximately 20 percent propagate proximally if left untreated[9] and these patients would be at serious risk for symptomatic pulmonary embolism.[1-3] Since the risk of bleeding with heparin is approximately 10 percent to 20 percent,[16,17] routine anticoagulant treatment of calf thrombi may result in a morbidity that is greater than the potential benefit. If the burden of hospital admission and subsequent sodium warfarin administration is added, then the risk to benefit ratio is even higher. It may be safer to abstain from anticoagulation and monitor extension of thrombi in these patients. Wheeler has advocated following patients suspected of DVT with negative IPG's, every 48 to 72 hours, as long as they are at risk for venous thrombosis. Using this approach, symptomatic pulmonary embolism occurred only once in 286 patients (0.3 percent) with normal IPG tests.[18] However, others feel that calf thrombi should be sought and treated, because they may give rise to emboli[15] and because the safety of withholding therapy has not been clearly shown.[10]

Nondiagnostic IPG

Of the two limbs in the present series that had non-diagnostic IPG studies, one was shown to have a calf vein thrombus and the other had a nonocclusive proximal thrombus. In Wheeler's larger group,[14] results in this indeterminate area of the graph included limbs that were normal, had calf vein thrombi or proximal vein thrombi. Patients with nondiagnostic IPG results probably should be studied by venography.

Areas For Investigation

IPG has been proposed as a method of following the course of a thrombus while the patient is receiving anticoagulation therapy.[19] Its usefulness in decision-making regarding duration of anticoagulation therapy, while reasonable, remains to be tested.

Proximal deep vein thrombosis has been thought to be the major source of pulmonary emboli found at autopsy.[2,3] Proximal deep vein thrombosis then is likely to be present in many

patients with pulmonary embolism, although symptoms of DVT may not be present. The actual incidence of DVT in pulmonary emboli has not been clearly shown in life because it requires carrying out venography and pulmonary angiography in sick, unstable patients. Recently, it has been reported that in patients with suspected pulmonary emboli, 90 percent of those with abnormal IPG had arteriogram-documented pulmonary embolism; conversely, of patients with negative IPG's, 90 percent had normal pulmonary arteriograms.[19] The potential predictive value of the IPG test result in patients with suspected pulmonary embolism warrants confirmation.

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Common Errors in Lavage

ICE WATER LAVAGE does lessen peptic bleeding—or delays gastric emptying, which aids in evacuating the stomach; and it cleans the stomach for panendoscopy. . . . The common errors in lavage are the following: too small a lavage tube, too little volume or lavage force, too short a duration of lavage and too much suction force. . . . So it should be vigorous inflow and very gentle outflow.

—J. LOREN PITCHER, MD, *El Paso, Texas*

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Refer to: Kuntz DH: Bedside diagnosis of urinary infection—A pilot study. West J Med 129:94-96, Aug 1978

Bedside Diagnosis of Urinary Infection

A Pilot Study

DAVID H. KUNTZ, MD, *Los Angeles*

Early recognition of catheter-associated urinary infection is essential to proper management. Daily bacteriological monitoring of indwelling catheters by routine urine culture is expensive and time consuming. A pilot study using liquid media at room temperature incubation showed a sensitivity approximating 90 percent in detecting bacteriuria. A simplified screening test can be carried out daily at the bedside; a positive screen would be followed by standard bacteriological studies. Such a method permits earlier diagnosis, and results in great saving in cost as well.

IN RECENT YEARS the incidence of urinary infection associated with indwelling catheters has been greatly reduced by aseptic catheterization, by emphasis on catheter care and by closed urinary drainage. Nevertheless, there is still significant morbidity and mortality from such infections. Therefore, it is important that catheter-associated urinary infection be recognized promptly so that appropriate treatment can be begun.

Kunin has recommended daily bacteriological monitoring of indwelling catheters.[1] Although this is the standard against which all other methods must be measured, daily urine culture suffers from several disadvantages:

- It is costly; at this writing, a negative urine culture costs a hospital patient in Los Angeles approximately $20; if the culture is positive, identification and sensitivity studies may bring the cost up to $40 or more.
- It is expensive in terms of personnel involved; after the physician orders the culture, the order is read by the nurse, then a designated person obtains the specimen by needle aspiration, transfers it to a suitable container and prepares an identifying label. Next someone transports the specimen to the laboratory where a bacteriologist inoculates, labels and incubates appropriate media. These are read at 24 and 48 hours, then a written report is prepared which then must be returned to the nursing floor and placed on the patient's chart. Only then are the results of the study available to the attending physician.
- Although most urinary pathogens show very evident growth within 16 to 18 hours, the report virtually never reaches the chart before 48 hours, and occasionally 72 hours may elapse before the written record is on the chart at the time the attending physician customarily makes rounds.

If a suitable screening test could be done at the patient's bedside, costs could be reduced and, even more important, recognition and treatment of urinary infection could take place a day or two earlier.

A number of chemical tests have been devised to detect infection. Those most commonly used in screening for urinary tract infection include the tetrazolium reduction test, the nitrate reduction to nitrite or Griess test, the glucose consumption test and the catalase test. Each of these methods

Dr. Kuntz is in private practice.

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Reprint requests to: David H. Kuntz, MD, 8540 Sepulveda Blvd., Los Angeles, CA 90045.

has a number of disadvantages in terms of false positives or false negatives which render it unsuitable for use in the detection of catheter-associated infection.[2,3]

Certain simplified bacteriological methods have been used in screening for urinary infection; most of these involve one or more bacteriological media in some format designed to simplify inoculation and reading; the best known of these is the dipslide. These tests have high reliability when compared with routine bacteriological testing, are capable of giving a quantitative answer, and in some cases indicate whether Gram positive or negative organisms are present. They have been used extensively and found reliable and effective with room temperature incubation.[4-6]

Other simplified bacteriological procedures can be used. Liquid media can serve as sensitive indicators of bacterial growth. Virtually all urinary tract pathogens ferment glucose and acidify the medium sufficiently to produce gross color changes if indicators are incorporated. Although pseudomonas does not ferment glucose, it does acidify the medium in the presence of air. All of these organisms grow readily at room temperature.

A pilot study was set up to test this method in two local hospitals. The medium used throughout was dextrose broth. In 41 instances purple broth with dextrose containing brom cresol purple, 15 mg per liter, as indicator, adjusted to a pH of 6.8 was used. This medium is purple initially, becomes yellow when acidified. For the remainder phenol red dextrose broth containing phenol red, 18 mg per liter, as indicator adjusted to a pH of 7.4 was used; this medium is red initially and turns yellow when acidified. The color change from purple to yellow was a bit easier to read than that from red to yellow; no other significant difference in the two media was noted.

All urine specimens sent to the laboratories for culture and sensitivity were cultured by the usual techniques (EMB agar and phenyl-ethyl agar using a 0.001 ml inoculum) and by the simple dextrose broth room temperature (DBRT) method. After inoculating the usual media the technician put two drops of the urine specimen in a tube of the special medium, numbered the tube and placed it in a rack at room temperature. The color of the medium was read and recorded twice daily. At the conclusion of the experiment the data obtained in this way were compared with the final bacteriological report. In all 164 consecutive specimens were tested. In 91 instances the laboratory reported no growth at 48 hours. The data on the positive cultures are displayed in Table 1.

TABLE 1.—*Organisms Found on Laboratory Cultures*

Organism Found on Culture	*Greater Than 100,000/ml*	*Less Than 100,000/ml*	*DBRT Positive by 12 Hours*	*DBRT Positive by 24 Hours*
Escherichia coli	29		26	28
		7	4	6
Enterococcus ..... (group D streptococcus)	6		6	6
		6	4	6
Proteus mirabilis	4		4	4
		2	1	2
Enterobacter	9		8	9
		1	0	1
Pseudomonas	1		0	0
		1	1	1
Staphylococcus ..... (coagulase negative)	1		1	1
		9	4	6
Candida albicans	3		1	3
		1	0	1
Alpha streptococcus .	3		1	2
		4	1	2
Gamma streptococcus (not group D)		4	3	3
Lactobacillus		1	0	0

DBRT = dextrose broth room temperature method.

Analysis

When the bacteriology laboratory reported over 100,000 organisms per ml, the DBRT test was positive at 24 hours 93 percent of the time; indeed it was positive at 12 hours over 80 percent of the time. Including all cases reported by the laboratory as showing bacteriuria, no matter how slight, 87 percent were positive by the DBRT test at 24 hours. In 13 cases the DBRT test was positive at 24 hours but the laboratory reported no growth at 48 hours. Possibly contamination may have occurred. However, it is likely that the larger inoculum (100 fold greater) and the use of a liquid nutrient renders the DBRT test more sensitive in detecting mild bacteriuria than the usual methods using solid media.

Discussion

Although the number of cases in this series is small the high correlation between the DBRT test and orthodox testing results suggests that this method may be valuable for the early detection of urinary infection related to indwelling catheters. Unlike the dipslide this method gives no indication of how many bacteria are present. However, in a patient with an indwelling catheter, all bacteria must be presumed to be of significance;

under the circumstances sensitivity becomes more important than the ability to give a quantitative answer. The mechanics of dipslide inoculation present some problems not present in the DBRT method. In addition, reading the dipslide requires more sophistication than recognizing the difference between yellow and purple. I selected dextrose broth because of its ready availability, ease of preparation and many years of use in the laboratory. However, modifications in the composition of the medium may increase its sensitivity, especially to the nonfermenting bacteria.

What I envision is a simplified method of bedside diagnosis of urinary tract infection incorporating these key features:

- Each patient with an indwelling catheter would have daily bacteriological "screening."
- The specimen would be obtained aseptically through the puncture port which is now an integral part of most closed drainage systems.
- This specimen would best be obtained in a device which incorporates aspiration and storage within itself so as to avoid having to transfer it to another container. Such a device (Pharmaseal Urine Sampling Unit) is now being manufactured by one company.
- Preferably this container would incorporate within itself a bacteriological indicator like the DBRT medium or a variant of the dipslide.
- The container would then be attached to the patient's drainage bag, thereby serving to identify it without having to label it.
- Each morning the previous day's specimen would be read at the bedside by inspection. If negative, it would be discarded and a new container inoculated.
- If positive, an orthodox urine culture would be inoculated and treatment could be begun while awaiting the definitive sensitivity studies. Perhaps a Gram stain done on the positive bacteriological screening test might serve as a valuable guide to such treatment.

The results of this pilot study suggest that such a regimen of bedside testing using the DBRT medium would probably detect bacteriuria within 24 hours of its appearance 90 percent of the time. If such a method were in use today the morbidity and cost of such infection should be greatly reduced.

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Refer to: Silverberg GD, Britt RH: Percutaneous radio-frequency rhizotomy in the treatment of trigeminal neuralgia. West J Med 129:97-100, Aug 1978

Percutaneous Radio-Frequency Rhizotomy in the Treatment of Trigeminal Neuralgia

GERALD D. SILVERBERG, MD, *and* RICHARD H. BRITT, MD, *Stanford, California*

A percutaneous technique of selective partial trigeminal root coagulation was evaluated in the treatment of 38 patients suffering from trigeminal neuralgia, 1 patient with pain secondary to oral carcinoma and 1 patient with atypical facial pain. The pain of trigeminal neuralgia was relieved in 94.7 percent of patients. Pain was relieved in the patient with oral carcinoma, but not in the patient with atypical facial pain. There was no mortality and no permanent morbidity outside of the trigeminal nerve lesion. The procedure requires only a brief hospital stay without the time, expense and hazards of open cranial surgical procedures.

TRIGEMINAL NEURALGIA (tic douloureux) is one of the most painful affiictions known to man. In order to relieve the sufferer, peripheral branches of the trigeminal nerve, the Gasserian ganglion and the trigeminal root have been interrupted surgically or by the injection of toxic agents.[1] Medications such as carbamazepine (Tegretol®) or phenytoin (Dilantin®) have reduced the frequency and severity of the pain attacks in many patients but with a considerable failure rate as well as a high incidence of unpleasant side effects.[2]

Although craniotomy with partial section of the trigeminal root or removal of compressing vessels affords lasting relief from trigeminal neuralgia, it does require a general anesthesia, open cranial surgical operation and a time-consuming and expensive hospital stay. A percutaneous technique has recently been introduced[3,4] that is as effective in relieving tic pain as the open surgical therapy. We have used this procedure in 40 patients at Stanford and have been impressed with its safety and effectiveness.

Method

The method we use differs only slightly from that previously reported.[3-6] The patient is brought to the operating room awake and alert. No premedication is used. A peripheral intravenous line is placed. Electrocardiograms and pulse are monitored. A portable image intensifier is positioned to give a true lateral picture of the skull. The appropriate side of the face and adjacent shoulder are prepared with betadine antiseptic. A point (A) is marked on the cheek at the intersection of a line dropped perpendicularly down the cheek from the inner edge of the pupil with a line joining the external auditory canal and the top of the nasolabial fold. A second point (B) is

From the Division of Neurosurgery, Department of Surgery, Stanford University Medical Center, Stanford, California.

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Reprint requests to: Gerald D. Silverberg, MD, Division of Neurosurgery (R155), Stanford University Medical Center, 300 Pasteur Drive, Stanford, CA 94305.

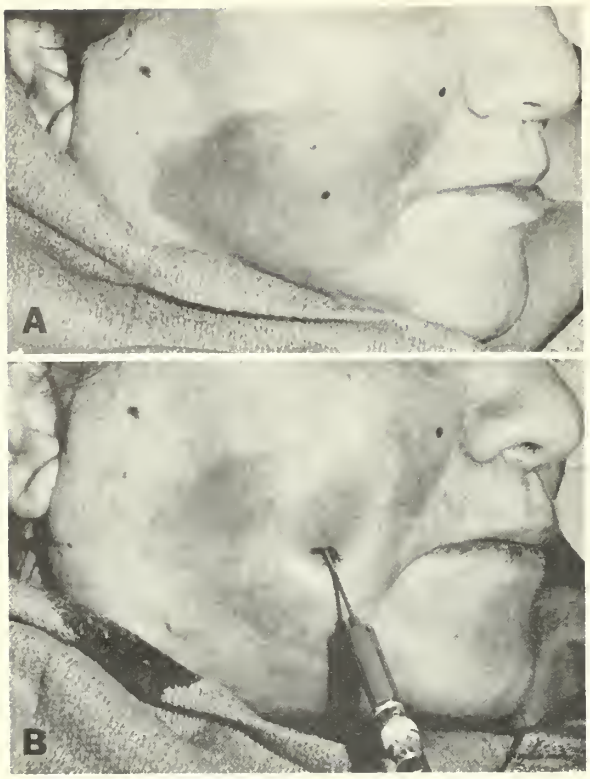


Figure 1.—A, The three coordinates are marked on the face of a patient. **B,** The needle electrode has been inserted and advanced along the coordinates to penetrate the foramen ovale.

marked 3 cm in front of the external auditory meatus. A point 2.5 to 3 cm lateral to the angle of the mouth is injected with a 0.5 percent solution of xylocaine and a xylocaine wheal is raised on the shoulder (Figure 1A).

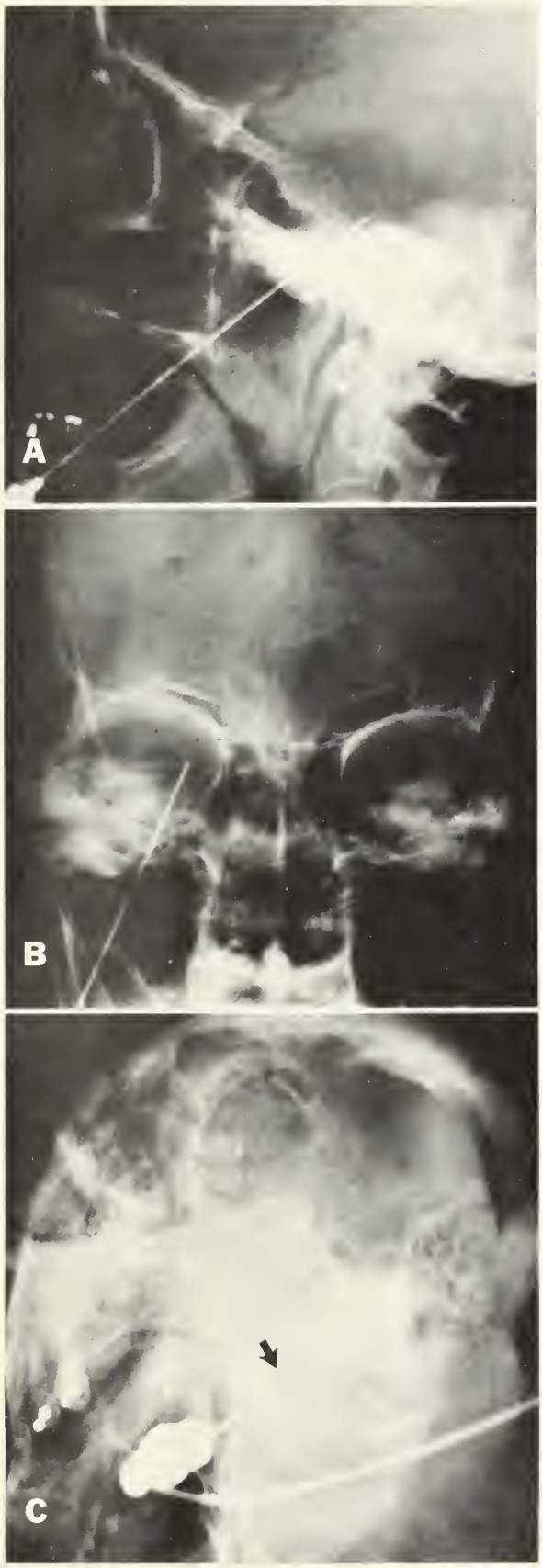
A disposable spinal needle inserted into the shoulder acts as the ground electrode. The patient is then briefly anesthetized with intravenous administration of methohexital (Brevital®), 30-60 mg., while a needle electrode (Radionics Type TIC Kit, Radionics, Inc., 76 Cambridge St., Burlington, MA 01803) is inserted at the point lateral to the corner of the mouth. A finger in the mouth guides the needle through the soft tissue of the cheek between the skin and mucous membrane as it is advanced medial to the ramus of the mandible towards the base of the skull. In order to penetrate the foramen ovale, the needle is directed towards a point at the intersection of lines projected posteriorly from point A in the sagittal plane and medially in the coronal plane from point B (Figure 1B). The needle is advanced under x-ray control through the foramen ovale toward the junction of the clivus and the petrous ridge as seen on the lateral fluoroscopic image (Figure 2A). As the needle is advanced, spinal fluid is usually encountered. The needle is positioned a few millimeters in front of the clivus for third division pain, at the clivus for second division and a few millimeters beyond the clivus for first division. The portable image intensifier is then rotated to check the needle position in the anteroposterior projection (Figure 2B) while the patient is waking up from the methohexital.

If there is any doubt as to the location of the needle, a submental vertex view is obtained to be certain the needle has penetrated the foramen ovale (Figure 2C). Repetitive pulse stimulation at 50 cycles per second with 200 to 500 mV (Radionics generator model RFG-3AV) will allow the patient to tell what portion of the nerve is being stimulated. After adjustment of the needle position, a graded destruction of the appropriate rootlets is carried out using a heat lesion. Use of 60°C for 60 seconds usually just starts a lesion that can be tested for with a safety pin. In most patients another dose of methohexital is needed, usually 20 to 40 mg, during this portion of the procedure.

Additional destruction, usually at higher temperatures for shorter periods, is frequently necessary to render the pain trigger zone and a portion of the appropriate division permanently hypalgesic. We use 70° to 75°C for 10 to 30 seconds with frequent testing of the patient's response to pinprick as a guide. After the initial lesion or two, pain sensation is frequently sufficiently dulled so that further increments of methohexital either are not required or are needed in a much reduced dose. We try to avoid dense analgesia, limiting the lesion to a blunted appreciation of the pinprick in the required areas.

Results

Forty patients with facial pain were treated with percutaneous radio-frequency rhizotomy and their conditions followed for from two months to three years. Of these patients, 38 had trigeminal neuralgia. One patient had atypical facial pain and the last suffered pain secondary to carcinoma of the tongue and floor of the mouth. The mean age was 63 years (range: 28 to 86 years). There were 12 males and 28 females. Pain was present on the right side in 20 patients and on the left side in 19. One patient with multiple sclerosis had bilateral facial pain.



Of the patients with trigeminal neuralgia, 19 had pain in a single division and 19 had pain in more than one division. The most common single division affected was V_2 (11 patients), but pain affecting both V_2 and V_3 was the most common combination seen (12 patients).

The average duration of trigeminal neuralgia was 8 years (range: 7 months to 25 years). Nearly all patients had previous treatment, including therapy with carbamazepine (37 patients), phenytoin (15 patients), alcohol blocks (18 patients), peripheral neurectomies (8 patients), craniotomy (4 patients), acupuncture (2 patients), and unsuccessful attempts at percutaneous rhizotomy at other institutions (2 patients).

Complete pain relief occurred in 37 of our 40 patients (92.5 percent) following percutaneous rhizotomy. In five patients (13.5 percent) a second lesion was required because of recurrent trigeminal neuralgia. This usually occurred two to eight weeks after the first procedure. A repeat lesion resulted in lasting relief of pain. Of the 38 patients with trigeminal neuralgia, 36 (94.7 percent) were finally relieved of their pain.

In three patients pain was not relieved by the procedure. In one woman with congenital scaphocephaly, we were unable to penetrate the foramen ovale because of a pterygoalar bar.[7] She subsequently had an open root section which has relieved her trigeminal neuralgia. In another woman with trigeminal neuralgia who had had previous neurectomies for V_2 distribution pain, we were unable to get pain relief despite an increase in numbness within the distribution of V_2. The patient with atypical facial pain was also not relieved by this procedure.

There were no deaths in this series. Thirteen patients were over the age of 70 and all tolerated the procedure well. There was one patient in whom the carotid artery was punctured. The needle was withdrawn and redirected more anteriorly and laterally to enter the foramen ovale rather than the foramen lacerum and the procedure continued. The patient's trigeminal neuralgia was relieved and there were no sequelae

Figure 2.—A, A lateral x-ray showing the needle electrode in position. Its tip lies just beyond the junction of the clivus and petrous ridge shadows. **B,** An anterior posterior projection showing the electrode just medial to the internal auditory meatus at the depression in the petrous ridge over which the trigeminal root courses. **C,** an oblique submental vertex view to show the electrode passing through the foramen ovale **(arrow).**

to the carotid puncture. In two patients cheek hematomas developed during the procedure, but there was no associated morbidity. The most serious complication was the development of a streptococcal meningitis one week after the procedure in a patient in whom the buccal mucosa was inadvertently punctured during passage of the needle to the foramen ovale. He was treated with antibiotics and recovered. Another patient had a mild aseptic meningitis secondary to a small amount of blood in the subarachnoid space following the procedure. There have been no cases of anesthesia dolorosa. Five patients had a decreased corneal reflex after the procedure, but none have had corneal complications. Two patients had significant ipsilateral masseter muscle weakness, both have since improved.

Discussion

It was initially hoped that by using a graded heat lesion, selective destruction of the pain-carrying A delta and C fibers within the trigeminal root could be accomplished with only minimal sensory loss.[4] Unfortunately, it has become apparent to us, as it has to others,[5-7] that there is a clear trade-off between the degree of analgesia produced by this procedure and the incidence of recurrent trigeminal neuralgia. The more restricted the sensory deficit, the higher the recurrence rate.

However, the more dense and widespread the anesthesia, the more likely it is that the patient will experience annoying or distressing dysesthesias in the area of numbness (anesthesia dolorosa). Since it is so safe and simple to treat recurrence by further percutaneous rhizotomy, while there is no effective treatment for anesthesia dolorosa, we initially make a small lesion which renders the trigger zone hypesthetic (blunting of a pinprick) without producing dense anesthesia. We accept that there will be an incidence of pain recurrence that will have to be treated by further rhizotomy.

The complications encountered have been gratifyingly few considering the age and associated medical problems of our patients. The one case of bacterial meningitis should not have occurred since it was clearly due to a break in technique. Fortunately, the patient's condition responded promptly to therapy with antibiotics and the patient recovered without sequelae. We had no mortality and no other significant morbidity outside of the trigeminal nerve. Of the complications involving the trigeminal lesion, the most dangerous is first division anesthesia leading to neuroparalytic keratitis. One tries to avoid significant first division sensory loss in any patient whose pain and trigger zone does not involve first division fibers, and with experience and patience, this can be achieved. The problem is in those patients with first division tic in whom a subtotal first division lesion must be made. For some reason, first division fibers seem to be more sensitive to the radio-frequency lesion than second or third division rootlets, and we have seen the lesion progress with remarkable rapidity in some of these patients. Fortunately, we have not yet had a case of keratitis occur. Weakness of the ipsilateral muscles of mastication is not an uncommon complication of the procedure. Curiously, patients do not seem to notice a unilateral motor loss. Regeneration is the rule and motor power improves with time.[5,8]

Damage to the carotid artery, the extraocular motor nerves and the ipsilateral temporal lobe has been reported by others.[5-8] Fortunately, these complications are extremely rare and usually occur only if the radiographic guidelines above are not rigidly followed.[6] As others have noted,[8,9] atypical facial pain is not helped by this procedure and it remains a treatment dilemma. In summary then, percutaneous radio-frequency trigeminal rhizotomy is a safe and effective treatment for trigeminal neuralgia, requiring only a few days in hospital. With experience and patience, pain relief can be achieved with only minimal risk and discomfort to the patient.

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Specialty Conference

Moderator
DAVID K. HENDERSON, MD

Discussants
DAVID K. HENDERSON, MD
DAVID B. TILLMAN, MD
HERBERT H. WEBB, MD
PHILLIP J. RAIMONDI, MD
ARTHUR A. SCHWARTZ, MD

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Infectious Disease Emergencies: The Clostridial Syndromes

DAVID K. HENDERSON, MD:* *This conference deals with a number of disease states caused by various members of the genus Clostridium. While these syndromes constitute a nonhomogeneous group, all of them require emergent recognition, prompt initiation of specific therapy and aggressive supportive care. We have chosen to discuss these syndromes as a group to focus on the extreme potency of the toxins elaborated by the clostridia, and to comment on specific and nonspecific measures which should be employed in the therapy of these syndromes. The syndromes to be discussed include botulism, tetanus and clostridial soft tissue infection.*

Before beginning our discussion of these clostridial emergency syndromes, perhaps we should first review a little of the bacteriology of these unusual organisms.

The clostridia are anaerobic, pleomorphic, spore-forming, usually Gram-positive bacilli. Most strains are strictly anaerobic, while a few are slightly aerotolerant. All clostridia form spores, some more readily than others; and most, but not all, are motile. These organisms reside primarily in the soil, and are nearly ubiquitous in distribution. Meyer, in his classic studies on botulism, found Clostridium botulinum in from 1 to 25 percent of all soil samples taken from several continents.[1]

The organisms upon which we shall focus our attention today share another feature in common —all of them produce potent exotoxins. These toxins are among the most highly lethal poisons known to man and are the major reason why the organisms and the disease states they produce remain some of the most feared in clinical medicine.

Botulism

DAVID K. HENDERSON, MD

History

ALL OF THE clostridial emergency syndromes have firmly established historical roots. The disease entity which is to be discussed first, botulism, is no exception. A summary of some of the historical highlights will be presented here. Should the reader desire more detailed historical information, several excellent reviews of this topic have been published.[1-4]

The clinical syndrome we know as botulism obtained its name because of its association with

*Division of Infectious Diseases, Harbor General Hospital, Department of Medicine, VA Wadsworth Hospital Center, Los Angeles; Assistant Professor of Medicine, UCLA School of Medicine.

From the Departments of Medicine and Surgery, Harbor General Hospital, Torrance, CA; the Division of Pulmonary Medicine, San Pedro and Peninsula Hospital, San Pedro, CA; and the Research and Medical Services, VA Wadsworth Hospital Center, Los Angeles.

Reprint requests to: David K. Henderson, MD, Division of Infectious Diseases, Department of Medicine, Harbor General Hospital, Torrance, CA 90502.

blood sausage in Germany in the late 1700's. Centuries earlier, in about 900 AD, Leo VI, an emperor of Byzantium, recognized blood sausage as being potentially lethal and forbade its consumption by his subjects. For this reason, according to Meyer,[5] he acquired the title "Leo the Wise."

In 1895 the Belgian microbiologist Van Ermengem first isolated the causative agent from salted, uncooked ham which had caused a neuroparalytic syndrome in 34 musicians.[4]

The myth that botulism was associated only with spoiled meat products was dispelled by separate outbreaks, both caused by contaminated beans, in Germany and in Stanford, California, in 1904 and 1913, respectively.[5]

A pronounced rise in the incidence of the disease paralleled the rapid growth of the commercial canning industry in the United States in the early 20th century. By 1919 a California botulism commission had been funded by the commercial canning industry and this resulted in the eventual development of safer canning procedures as well as legislation to guarantee them. Since that time, sporadic outbreaks of botulism have occurred, usually traceable to home-canned, dried or smoked, poorly processed, or poorly prepared foods. The outbreaks caused by commercial foods have usually been traceable to errors in processing or storage of the food.

Bacteriology

Eight toxigenic serotypes of C botulinum exist (types A, B, $C\alpha$, $C\beta$, D, E, F and G). The organisms are classified by the toxins they produce. Types A, B, E and F have been shown to produce disease in man. The organisms produce their toxins while in the vegetative state in a environment of pH 4.6 to 5.3.[3] These organisms, many of which require some vitamin and amino acid supplementation for propagation on artificial media, all require strict anaerobic conditions for growth. Complete absence of oxygen may not be necessary for toxin production. C botulinum spores are able to withstand surprising amounts of heat, drying, freezing, ionizing radiation and chemical exposure.[4] The spores themselves may contain minute amounts of toxin.

Toxin

The toxins elaborated by C botulinum are extremely potent. Jensen notes that the lethal dose of type A toxin for white mice may be as little as 10^{-13} grams per kg of body weight, or about 950 molecules of toxin per mouse.[6] The toxins are proteins and, with the exception of the type C strains, are serologically distinct. Antitoxin to type $C\alpha$ neutralizes the toxins of both the $C\alpha$ strains as well as the $C\beta$ toxin; while antitoxin to the toxin produced by the $C\beta$ strain neutralizes only $C\beta$ toxin. The toxin is not destroyed by the process of gastrointestinal digestion, and, in fact, may be potentiated in the process of digestion and absorption—presumably due to the action of nonspecific proteases in the stomach cleaving the toxin to a more active form.[7-9] The toxins are heat labile and are inactivated by boiling for six to ten minutes, but are otherwise reasonably stable, withstanding wide variations of pH, chemicals and ionizing radiation.[3]

The toxins are rapidly absorbed from the gastrointestinal tract and rapidly become bound to neural tissue, probably by transport via the bloodstream or the lymphatics.[10] The toxins act at the level of the neuromyal junction. Release of acetylcholine is inhibited from the terminal axons producing a neuroparalytic syndrome similar to that induced by hypermagnesemia, hypocalcemia, aminoglycoside toxicity and the Eaton-Lambert syndrome.[11] Several investigators have studied nerve conduction and stimulation and have found that repetitive stimuli (25 to 50 stimuli per second) resulted in facilitation of the action potential of the affected muscles (posttetanic facilitation). This situation is not unique in clinical medicine and roughly parallels the electrical findings in the Eaton-Lambert syndrome.[12] The amplitude of the facilitated action potential, however, has been found to be less than normal, unlike the Eaton-Lambert syndrome.[11]

Kao and co-workers have further documented the blockade of acetylcholine release and suggested that the block may be at the level of exocytosis of acetylcholine granules from the terminal axons.[13]

The various toxins differ widely in their affinity for neural tissue. Type A toxin is the most tightly bound, type E next and type B the least well bound. The variations in binding relate inversely to the facility with which the toxin may be recovered from the serum (that is, those toxins that are poorly bound remain in the serum longer). The toxins which continue to circulate are, therefore, more readily available for neutralization by antitoxin.

TABLE 1.—*Frequency of Botulism Cases in the United States, 1899-1973, by Serotype**

Type	*All Cases (Percent)*	*Cases with Identifiable Serotype (Percent)*
Type A	23.1	69.4
Type B	6.3	20.0
Type E	3.2	9.4
Type F	0.1	0.4
Types A and B	0.3	0.8
Untypeable	66.7	....

*Modified from data accumulated by the Center for Disease Control.[14]

Epidemiology

According to the Center for Disease Control (CDC) in Atlanta, 688 outbreaks of botulism (1,784 cases) have occurred in the United States from 1899 to 1973.[14] Both the incidence and the fatality rate climbed steadily until the 1940's. From the early 1940's until 1970 the incidence fell from nearly 40 cases per year to fewer than 20. In the 1940's, mortality occurred in more than 60 percent of all cases. By the 1960's, the incidence and the fatality rate had dropped to nearly 25 percent.[14] Since the 1960's the incidence and the fatality rate have remained fairly constant.

Vegetables have become the most commonly implicated source in food-borne botulism. Vegetables accounted for 17.4 percent of all outbreaks reported, while meats, including fish and poultry, accounted for only 6.1 percent.[14] Of the 688 outbreaks reported from 1899 to 1973, nearly 67 percent could not be traced to any contaminated food source. If the cases in which no identifiable source can be documented are eliminated, vegetables account for more than 50 percent of the remaining cases.

Nearly two thirds of the cases summarized by the CDC were untypeable. The frequency of botulism cases by serotypes is presented in Table 1.

Type A remains the most common serotype seen in clinical disease. Also of interest is the fact that there is a geographic variation in both the frequency of cases seen and in the serotype found. Type A, for instance, is most commonly found in the western United States. Approximately 90 percent of all cases of type A botulism occurring in the United States are found west of the Mississippi River.[14] Of the cases of type B botulism, 67 percent are found east of the Mississippi.[14] More than a third of all cases occurred in California. The reason for the high incidence of botulism in California is unclear. Werner and Chin have postulated that a heightened awareness of the disease or possibly a higher concentration of the spores of C botulinum in the soil of California might account for this increased incidence.[15] Type E botulism has been most closely associated with fish and marine products. Most cases of type E botulism in the United States have occurred in Alaska and in states surrounding the Great Lakes.[14] Type F botulism is extremely rare. Only two outbreaks in humans have been reported,[16,17] and one of these outbreaks occurred in California. Additionally, one outbreak each of types Cα and type D botulism in humans was reported by Dolman.[4]

Diagnosis

Symptomatology

Symptoms of botulism are relatively specific and usually suggest the diagnosis early in the course of the disease. Unfortunately the diagnosis is frequently missed early in the development of the disease since it is relatively uncommon and most physicians have a low index of suspicion. The onset of the disease usually occurs between 12 and 48 hours after the ingestion of contaminated food. Rapid onset of the disease (that is, development of symptomatology in less than 24 hours after ingestion) is a poor prognostic sign and predicts a more severe illness with a more protracted course and a higher fatality rate.[18] Cranial nerve symptoms, most commonly relating to the extraocular muscles (diplopia, ptosis and blurred vision), pharynx (dysphagia, pharyngeal pain), or larynx (dysphonia) are among the most common specific presenting symptoms. These presenting complaints are commonly followed by the development of a symmetrical descending paralysis which affects all muscle groups but spares the sensorium.

In addition to the above symptoms, other common presenting manifestations of botulism include nausea, vomiting, abdominal pain, abdominal cramping, early diarrhea, late constipation, dizziness and occasionally symptoms of urinary retention.

Physical Findings

The CDC lists five cardinal features of botulism.[14] They are as follows: (1) fever is absent, (2) mental status is normal, (3) the pulse rate

TABLE 2.—*Wound Botulism**

No epidemiologic evidence for food contamination.
There is an apparent wound source of the organism.
Gastrointestinal symptoms are uncommon.
Fever may be present (secondary to wound infection).
The incubation period is slightly longer (4-14 days).
Toxin may be identified in both the serum and the wound.
Wound cultures may be positive for Clostridium botulinum.

*After Merson and Dowell.[24]

is normal or slow, (4) sensory deficits are absent and (5) neurological manifestations are symmetrical.

A few of these cardinal features may be masked by concurrent problems. Fever, as well as tachycardia, may be present if a patient has developed a complicating infection, such as aspiration pneumonia or urinary tract infection. Mild alteration in the mental status may be noted. The patient may be agitated, combative or drowsy; but most patients are arousable and oriented.

Nearly three fourths of the patients reviewed by the CDC had respiratory embarassment, almost half had specific muscle paresis and nearly half had involvement of the eye muscles.[14] Less common findings from this series included pupillary findings, dry mucous membranes, cerebellar findings and postural hypotension.[14]

Laboratory Diagnosis

General laboratory evaluation in botulism is of little value. Most of the routine screening procedures are not affected by the disease. The blood count, urine analysis, cerebrospinal fluid evaluation and serum electrolytes are all normal.

Radiographic findings are not generally helpful as well, with the possible exception that an early ileus due to botulism may be present on an abdominal film.[19]

The electrocardiogram (ECG) is frequently abnormal, but is usually nonspecific. Abnormalities one may see on the ECG include nonspecific ST segment changes and T-wave inversion. Occasionally botulism may cause a pattern on the ECG that is indistinguishable from inferior infarction.

An extremely helpful laboratory aid in the diagnosis of botulism is the electromyogram (EMG). Several investigators have stressed the importance of showing posttetanic facilitation of the muscle action potential. At least one group of investigators has suggested that this facilitation, while similar to the electrical findings in the Eaton-Lambert syndrome, is specific enough to assist in confirming the diagnosis of botulism.[11]

Cherington has also noted the phenomenon of posttetanic facilitation in patients with botulism.[20] Additionally, he notes that less frequent stimuli (that is, a rate of two stimuli per second) resulted in a decrement in the recorded action potential. In this paper the author also notes that the onset of the electrical abnormality may lag behind the early symptomatology of botulism, and that the degree of posttetanic facilitation which occurs relates directly to the severity of the disease.[20]

By far the best way to confirm the diagnosis of botulism in the laboratory is by demonstrating the presence of toxin in the affected patient. Classically, clinicians have examined serum and incriminated foods for the presence of the toxin by using the mouse neutralization test.[21] Mice are protected with type-specific antisera and then injected intraperitoneally with samples from chemically suspect material.

Recent attention has focused on stool specimens as a fairly reliable source of toxin in patients with clinical botulism.[22] Therefore, when the diagnosis of botulism is suspected, samples of serum, gastric contents, stool and epidemiologically incriminated foods should be sent immediately to the nearest reference laboratory for confirmation. In addition, physicians should notify local, state and federal public health officials.[23]

Wound Botulism

Two other clinically distinct syndromes caused by C botulinum deserve our attention. The first, wound botulism, was reviewed in some detail by Merson and Dowell in 1973.[24] These authors reviewed nine cases of botulism resulting from wounds contaminated with C botulinum and outlined the difference in clinical presentation of wound botulism from classical, food-borne botulism. The salient features of wound botulism are outlined in Table 2. The absence of gastrointestinal symptoms, the clinical signs of wound infection (for example, fever and induration), and the frequent finding of the organism or the toxin in the wound are obvious differences in the clinical syndromes. All of the cases reported by Merson and Dowell were either untyped or type A. This alone could account for the paucity of gastrointestinal symptoms. After the acquisition of the toxin, however, patients develop the characteristic clinical syndrome with the classical electrical findings of botulism.[24]

TABLE 3.—*Therapy of Botulism*

Administration of antitoxin.
Elimination of persistent organisms.
Supportive care.
Pharmacologic manipulation.

Infant Botulism

A third and more recently identified syndrome of botulism is infant botulism. This syndrome, unlike the classical food-borne illness, probably results from the ingestion of spores of C botulinum. The spores germinate in the gut of the infant and subsequently produce their toxin *in vivo*. The clinical presentation is that of neuromuscular paralysis. Constipation is a frequent presenting complaint with subsequent development of weakness, lethargy and hypotonia. Death has been attributed to respiratory insufficiency. Infants under six months of age are most commonly affected, and the diagnosis can be established on the basis of clinical presentation, the characteristic electromyogram, and showing the presence of the toxin in serum, and particularly in stool specimens.[25] The causative agent may also be cultured from the stool or gastric aspiration. The incidence of this newly recognized syndrome is not certain, although one preliminary estimate from the California Department of Health suggests 100 cases a year may occur in California.[26]

Differential Diagnosis

While the clinical syndrome of food-borne botulism is fairly specific, several different disease states are frequently confused with botulism. Of the 438 suspected outbreaks of botulism reported to the CDC in a recent ten year period, 75 (17.1 percent) were subsequently confirmed as outbreaks of botulism.[14] Other than botulism, the most common final diagnoses in these cases include Guillain-Barré syndrome, chemical intoxication and food poisoning.

The presence of fever and abnormal cerebrospinal fluid findings should help exclude botulism and suggest one of the viral encephalitides. The presence of focal neurologic symptoms or findings should suggest a mass lesion or midbrain stroke syndrome. Paresthesias suggest the Guillain-Barré syndrome (along with its characteristic ascending paresis), tick paralysis, and shellfish poisoning. Rapid onset (that is, the development of symptoms within minutes or hours after ingestion) should suggest chemical intoxication, shellfish or mushroom poisoning. Chemicals likely to be implicated in poisonings of this sort include carbon monoxide, barium carbonate, organic phosphates, methanol and atropine.

Myasthenia gravis can be distinguished on the basis of muscular fatiguability, a positive response to intravenous injection of endrophonium chloride and nerve conduction studies that show decreasing amplitude of the action potential with repetitive stimuli.

Diarrhea without subsequent cranial nerve involvement is most likely to be due to Staphylococcus, Shigella, Salmonella, toxigenic Escherichia coli, Clostridium perfringens, or other bacterial pathogens.

In addition, several antibiotics have been noted to cause a neuroparalytic syndrome after administration, especially following the induction of general anesthesia. Nearly all of the aminoglycosides, polymyxins and bacitracin have been implicated in this syndrome.[27]

Therapy

The principles for managing patients with clinical botulism are outlined in Table 3.

All patients with clinical botulism should be admitted to an intensive care area of the hospital, evaluated and treated promptly. Samples of serum, gastric contents, stool and incriminated foodstuffs should be obtained and sent to a reference laboratory. Patients should be skin tested for horse serum sensitivity, and if it is present, desensitized as quickly as possible. If the toxin type is unknown, trivalent antitoxin, containing antitoxin to types A, B and E should be administered. The trivalent antitoxin is manufactured by Connaught Laboratories of Toronto, Ontario, Canada. This preparation is available either from the California State Health Department or from the CDC. The contents of one vial should be administered intravenously every four hours for a total of four or five doses.[15] Since some toxins have been shown present in the serum as late as several weeks after ingestion, continued monitoring of the serum (especially in type B botulism) for the presence of toxin is advisable. If subsequent toxin is detected in the serum, more antitoxin should be administered.

If the outbreak is known to be caused by organisms of type A or B, a bivalent preparation is commercially available from Lederle Laboratories, Los Angeles. Monovalent Type E anti-

toxin is also available from the CDC in the event of a known type E outbreak.

In the unlikely event that the clinical botulism is found to be caused by types C, D, F, or G organisms, polyvalent antitoxin manufactured by the Serum Institute of Denmark is available from the CDC.[14]

The patient's condition should be monitored closely. The gastrointestinal tract should be emptied. This can be accomplished by inducing emesis, lavage, cathartics and high enemas in appropriate patients. Incipient paralysis is a clear contraindication to the use of emetics, and the presence of bowel atony or ileus should mandate against the use of cathartics.

Some investigators have advocated the use of antibiotics, usually penicillin.[28] The efficacy of antibiotics in food-borne botulism has not been established.

Careful pulmonary management of patients with neuroparalytic syndromes has probably been one of the major contributing factors to the lowered mortality due to these diseases since the 1940's. Other adjunctive therapies should include attention to the patient's bowel habits, cardiac status, muscle tone, integumentary system and nutritional status. Prophylactic low dose heparin may be of value in preventing the complications of thrombophlebitis and subsequent pulmonary embolism. Cardiac monitoring is essential because of the propensity for this disease to terminate in sudden death—probably due to cardiac arrhythmias. Decubitus ulceration may be a cause of sepsis and death in chronically bedridden patients,[29] and careful attention to positioning and physical therapy can help prevent ulceration as well as other musculoskeletal complications such as contractions. Parenteral hyperalimentation may be advisable in some patients to increase their caloric intake.

Several drugs have been tried in an attempt to reverse the blockade of acetylcholine release. Of those tried, guanidine hydrochloride has received the most attention. Several case reports have appeared suggesting some beneficial effect of the drug in clinical botulism,[30,31] and several failures have been reported as well.[32,33] Its use remains controversial and attempts to use the drug should be accompanied by careful monitoring of objective clinical measures of the disease. Side effects of guanidine include nausea, vomiting, paresthesias, fasciculations and rare idiosyncratic reactions including bone marrow toxicity.

In cases in which wound botulism is suspected, all of the above modalities should be employed. After the administration of the antitoxin, aggressive debridement and drainage of the wound should be carried out.[24] Penicillin should also be administered, though again its efficacy has not been proved.

Proper management of infant botulism has not been completely delineated. Patients should be given antitoxin, although its efficacy in this new clinical syndrome has yet to be established. Gastrointestinal evacuation should be carried out unless ileus is present, and patients should be given supportive care. The possibility that antibiotics, administered either by the oral or parenteral route, may be of value is still theoretical.

The management of asymptomatic patients with possible exposure to botulism is less certain. If the patient is known to have consumed contaminated food and presents within one week of the ingestion, he should be admitted, evaluated and treated with antitoxin. The diagnostic studies outlined above should be carried out and adjunctive therapy administered as the clinical course dictates.

If it is not certain whether the patient has consumed contaminated food, and he remains asymptomatic, the patient should be admitted to the hospital for observation. The gastrointestinal tract should be emptied and serum, stool and gastric contents sent for diagnostic studies.

The decision whether to administer antitoxin is a difficult one, and the possible complications of the antitoxin (for example, anaphylaxis or serum sickness) should be weighed carefully. At the first sign or symptom suggestive of botulism, it is advisable to administer the antitoxin.

Finally, I should emphasize that the care of a patient with botulism is dependent on careful planning and attention to detail. All the people involved in the care of the patient—nurses; primary physicians; consultants in pulmonary medicine, infectious diseases and otolaryngology, and physical therapists—should plan the patient's therapy and each should be fully aware of the continuing therapeutic plan.

The second clostridial syndrome to be discussed is tetanus. As indicated by the following description, tetanus has firmly established historical roots as well.

Tetanus

DAVID B. TILLMAN, MD*

History

"THE MASTER of a large ship mashed the index finger of his right hand with the anchor. Seven days later a somewhat foul discharge appeared; then trouble with his tongue—he complained he could not speak properly. The presence of tetanus was diagnosed, his jaws became pressed together, his teeth were locked, then symptoms appeared in his neck; on the third day opisthotonos appeared with sweating. Six days after the diagnosis was made he died."[34] This accurate clinical description of tetanus by Hippocrates dates to 400 BC. Over the next 22 centuries many theories regarding its origin were proposed. It was not until 1884 that Nicolaier showed its infective nature by producing tetanus in animals that he had injected with soil. By 1897 Nocard showed the protective effect of antitoxin, and passive immunization was used on a large scale during World War I. Tetanus toxoid was developed in the 1920's and was used almost universally during World War II. The advances made in controlling tetanus are most dramatically illustrated by examining the incidence during war. Because wounds contaminated by soil are such a common battlefield occurrence, tetanus has always been a prominent feature of war. During the Peninsular War in Spain from 1808 to 1814, British soldiers contracted tetanus at a rate of 12.5 cases per 1,000 wounded. On the western front during World War I (1914 to 1918) where passive immunization was available, the rate dropped to 1.47 cases per 1,000 wounds. During World War II the United States Army actively immunized all soldiers. The rate was 0.0062 per 1,000 wounded (one case of tetanus in 160,254 wounded).[35] The availability of tetanus toxoid has had striking impact and made tetanus a preventable disease.

Etiology

Clostridium tetani is a slender, motile, Gram-positive anaerobic rod. It exists in both a vegetative and a sporulated form. The sporulated form is characteristically drumstick-shaped in appearance, with the spore at one end of the rod. The vegetative forms are susceptible to heat and to a variety of chemical agents while the spores are highly resistant to boiling, antiseptic agents and even autoclaving at 120°C for 15 to 20 minutes. Both forms are ubiquitous in nature and may be found in the feces of domestic animals and humans, in operating rooms and house dust, and in contaminated heroin.[36]

Acquisition of the organism, usually the sporulated form, is the first event in the sequence leading to tetanus. Because the organisms do not possess any special ability to invade the body tissues, some traumatic injury often precedes infection.[37] The spores must also be converted into the vegetative form. This transformation will occur only under certain circumstances—for example, introduction of a foreign body or the development of suppuration—which reduces local oxidation-reduction potential. Only after the vegetative form begins to proliferate and produce tetanospasmin does disease occur. The incubation period is usually 3 to 21 days, but it can be as short as one day or as long as several months.

Tetanospasmin acts on several areas of the nervous system. Its primary effect is on the spinal cord leading to dysfunction of inhibitory polysynaptic reflexes; this action accounts for the spasm seen in tetanus.[38,39] The toxin also acts on the sympathetic nervous system,[40] resulting in labile hypertension, tachycardia, cardiac arrhythmias, diaphoresis or fever. A third site of action is at the level of the neuromyal junction resulting in interference with neuromuscular transmission by inhibiting the release of acetylcholine.[41] The clinical importance of this effect is not known.

Clinical Manifestations

The first clinical manifestation of tetanus is trismus in over 50 percent of the cases.[36] Persistent trismus produces a characteristic expression, the risus sardonicus. The trismus may be replaced by stiffness of the neck or other muscles, difficulty swallowing or rigidity of the abdominal muscles. Intense, persistent spasm of the back musculature can result in opisthotonos. Tetanic "seizures" are characterized by a sudden painful burst of tonic contractions causing opisthotonos, flexion and adduction of the arms, and extension of the lower extremities.

In addition to generalized tetanus described above, syndromes of both local and cephalic tetanus may occur. Local tetanus is characterized by persistent rigidity of the muscle groups in close proximity to the site of injury and carries a low mortality. Cephalic tetanus is an unusual form of the disease with a short incubation period follow-

*Fellow, Division of Infectious Diseases, Harbor General Hospital, Torrance, California.

ing injuries to the head. While generalized tetany may occur, usually this form of the disease is characterized by involvement of the 3rd, 4th, 7th, 9th, 10th and 12th cranial nerves.

The diagnosis of tetanus is made clinically; a Gram-stain and anaerobic culture of material obtained from a wound may be negative. The diagnosis of the disease is based primarily on a history of injury followed by the development of one of the syndromes described above. It is important to remember that the organism may grow in any type of wound. This includes burns and surgical wounds. During the past year we have seen a case of tetanus in a woman in whom a gangrenous leg had been amputated.

No disease fully resembles tetanus, so the differential diagnosis is brief. Strychnine poisoning may closely mimic tetanus, but the strychnine will be detectable in the urine. Early in its course the combination of fever and neck stiffness may suggest meningitis. A lumbar puncture is normal in tetanus, however, so meningitis can be easily ruled out.

Treatment

The therapy of tetanus involves two major principles. The first is neutralization of circulating toxin and elimination of the organism. Human immune globulin (TIG, tetanus immune gobulin) is now universally available. The recommended dose is 3,000 to 10,000 units given once intramuscularly,[42] although there is evidence that as little as 500 units may be as effective.[43] Retrospective analysis has shown a lower case-fatality ratio in patients treated with antitoxin than in those who did not receive antitoxin.[43]

Surgical debridement and penicillin therapy (1,000,000 units given intravenously every six hours) will help eliminate the infecting organism and, therefore, will stop the production of any new toxin. Tetracycline should be used in patients allergic to penicillin.

The second major principle of therapy concerns constant support of the patient. Antitoxin does not affect tetanospasmin already bound to nerve tissue. It is necessary to support the patient for the days to weeks it takes for the toxin to be eliminated. The patient should be kept in a quiet environment to minimize spasms and generalized seizures. Rigid attention should be paid to skin and bladder care. Because of the work associated with the muscular contractions, insensible water loss may be high. For this reason, strict monitoring of fluids and electrolytes is mandatory. These patients consume thousands of calories because of this muscular work. Some authors suggest nasogastric feedings while others express fear of aspiration. Parenteral nutrition must be considered, as nitrogen loss can be significant.[50] Because the muscular spasms may involve the upper airway and because these patients have great difficulty with their secretions, tracheostomy is frequently necessary. While this procedure should not be done routinely, as soon as airway problems become evident, a tracheostomy is indicated.[36]

Sedation and control of the spasms are also mainstays of therapy. Diazepam is very effective because it both sedates the patient and reduces spasm.[44] Large doses, up to 20 mg every two hours, may be necessary. Other drugs which are used include secobarbital sodium, chlorpromazine and meprobamate. (All act to both sedate the patient and to eliminate spasms.) As with diazepam, the dose or combination of drugs that is required may be one that is toxic for normal people.

Although fever may be secondary to sympathetic nervous system involvement or to the heat generated by extremes of muscular activity, infection must be considered with each temperature elevation. In these patients aspiration pneumonia, skin infections or urinary tract infections are likely to develop, especially if the urinary tract is instrumented.

Prevention

Even with the widespread availability of antitoxin and the use of intensive care units, the mortality of tetanus remains in excess of 40 percent.[36,45] Of the 102 cases of tetanus reported in 1945, a total of 45 (44 percent) resulted in death.[46(pp2-4)] It seems evident, therefore, that preventing the disease is the most efficient way to eliminate these deaths. This can be accomplished through proper immunization of both children and adults. Primary immunization is of great importance. In children, this means diphtheria-pertussis-tetanus (DPT) given intramuscularly on four occasions, with three doses at four to six week intervals and a fourth dose approximately one year later. This series should begin at two to three months of age. In adults, a series of three doses of adult type tetanus and diphtheria toxoids should be given. The second dose should follow the first by about six weeks with the last coming six months to one year later. Boosters

TABLE 4.—*Guide to Tetanus Prophylaxis in Wound Management**

History of Tetanus Immunization (doses)	*Clean, minor wounds*		*All other wounds*	
	Toxoid	*TIG*	*Toxoid*	*TIG*
Uncertain	yes	no	yes	yes
0-1	yes	no	yes	yes
2	yes	no	yes	no†
3 or more	no‡	no	no§	no

TIG = Tetanus Immune Globulin

*Modified from reference 42.
†Unless wound more than 24 hours old.
‡Unless more than 10 years since last dose.
§Unless more than 5 years since last dose.

should be given to children upon entering school and then every ten years. Except as noted below, more frequent boosters are not indicated and may be associated with increased incidence and severity of reactions.[47]

The correct use of tetanus toxoid and immune globulin is important for tetanus prophylaxis in the management of wounds. Persons with clean, minor wounds should receive a primary vaccination series if they have never received one. If a patient has been previously immunized, but more than ten years have passed since last receiving toxoid, then a booster is indicated. Tetanus immune globulin is not needed. The above holds true for dirty wounds, but a cutoff of five years should be used in deciding whether or not to give a booster to those with previous immunization. Tetanus immune globulin should be administered if any of the following criteria are met: previously unimmunized patients, patients with fewer than two previous doses of tetanus toxoid who have large or contaminated wounds, patients presenting with a wound which is more than 24 hours old who have had fewer than three doses of toxoid. These data are summarized in Table 4.

The amount of tetanospasmin that induces tetanus is not sufficient to stimulate an immune response. For this reason, it is important to remember to fully immunize any patient with tetanus.

Clearly, the best prophylaxis against tetanus involves routine immunization and boosters every ten years. It should be a part of each physician's routine to make sure that his patients are adequately immunized. This includes the elderly as well. In 1976 the incidence of tetanus was greatest in patients over 50 years old.[46(p62)] Another group in whom immunization is extremely important is heroin users. As noted above, C tetani has been found in heroin.[36] Heroin addicts are routinely violating their skin and creating minor wounds. Women addicts, in particular, may destroy their veins and begin to inject subcutaneously ("skin pop"). This produces an anaerobic environment which will allow vegetative forms to grow. Additionally, many men enter the military and receive routine immunization as young adults. Women, not having served in the military, may not have received primary immunization or recent boosters. Once it develops, tetanus in heroin addicts is usually severe and has a high mortality rate.[48]

In summary, tetanus is a severe neuromuscular disease produced by an exotoxin of Clostridium tetani. Therapy involves administration of antitoxin and supportive management of the patient. Prevention through immunization is effective and inexpensive, requiring only primary immunization and then boosters every ten years. Proper immunization and wound management combine to make tetanus an easily preventable disease.

While specific therapy for both botulism and tetanus has been developed, the decrease in mortality and morbidity seen in both syndromes over the past 15 years is primarily due to pronounced improvement in nonspecific supportive care of patients with severe neuromuscular diseases. The cornerstone of this supportive care is careful respiratory management of these patients. Because the pulmonary care is so important we have asked Dr. Herbert Webb to discuss this subject in depth for us.

Respiratory Care of Tetanus and Botulism

HERBERT H. WEBB, MD*

IT IS APPROPRIATE to discuss respiratory care of patients with these diseases in some detail since the majority of fatalities in clinical tetanus and botulism, as in many neuromuscular diseases, results from pulmonary complications. Moreover, these problems can be anticipated, prevented, and treated in the modern intensive care unit with adequate equipment and, most important, a competent respiratory care team.[50-53] The team must consist of an experienced, knowledgeable and readily available physician who guides the team of nurses and respiratory therapists with fore-

*Director of Pulmonary Medicine, San Pedro and Peninsula Hospital, San Pedro, California, and Associate Clinical Professor of Medicine UCLA.

knowledge and an attitude of constant vigilance and encouragement.

Respiratory aspects of the care of these disease states encompass much of modern respiratory diagnostics and therapeutics as covered in excellent monographs.[51-53] Problem categories include upper airway obstruction, subtle and overt aspiration, atelectasis, pneumonia, pulmonary embolism, and technical failure of respiratory support devices. If the total care team effectively meets these challenges along with the general care of the paralyzed patient the vast majority of tetanus and botulism victims will recover from these self-remitting clostridial diseases.

Experience has shown it to be essential, especially for tetanus, to anticipate the severity and rate of progression from the initial meeting of the patient.[54] Such schemata most effectively utilize the period of onset (time from first symptom to first spasm) as a major guide. If this period is three days or less, the disease is severe; if three to six days, moderate; and more than six days, mild. In severe tetanus, therapy with paralytic agents and mechanical ventilatory support will be necessary. In moderate tetanus an artificial airway as well as pharmacologic control of spasms will usually suffice. Only the latter may be needed in mild tetanus.

Also, objective measurements of ventilatory mechanics as well as gas exchange should be made serially in conjunction with clinical observations early in these diseases to determine need for artifical airway and ventilatory support before a crisis occurs. Criteria for instituting respiratory support include a vital capacity of less than 15 ml per kg of body weight, any elevation of arterial carbon dioxide tension, and maximum inspiratory pressure against a closed manometer system of less than 25 cm of water (the inspiratory effort starting from residual volume).[55] I like to include the simple but valuable observation of cough effectiveness (at expelling secretions completely). Black and Hyatt[56] found that maximum pressure measurements are more sensitive than vital capacity and expiratory flow measurements in detecting subtle neuromuscular limitation of the respiratory bellows. They showed the usefulness of pressure determinations in the presence of coexistent lung disease and provided an excellent discussion of the physiology involved.[56] Of course, arterial blood gas measurements determine both respiratory failure of oxygenation and ventilatory failure of carbon dioxide elimination and are essential to the management of these patients in all stages.

Upper airway obstruction requires swift intervention in both diseases under discussion. This results from muscle weakness of pharyngeal, laryngeal and thoraco-abdominal muscles in botulism or from laryngeal or pharyngeal spasm in tetanus. The latter may evolve abruptly in severe tetanus and it is crucial to rapidly give a large intravenous dose of a paralytic agent or muscle relaxant (preferably diazepam) to facilitate tracheal intubation. In both diseases aspiration of secretions or food can also cause upper airway obstruction. Most clinicians experienced in dealing with the early stages of tetanus recommend early endotracheal intubation under anesthesia or perhaps paralytic agent coverage, followed by tracheostomy. The logic as well as the safety of this approach centers on the necessity of reversal of thoracic and abdominal muscle spasms to allow effective ventilation regardless of the type of airway or the rapidity with which it is placed.

Of course, tetanus contrasts with botulism in that the rigidity and spasm of trunk muscles causes ventilatory failure, whereas, in botulism respiratory muscle paresis or paralysis is the problem. Several pharmacologic agents may control moderate tetanic spasms. Diazepam is the current favorite in the United States.[57,58] It may be combined with chlorpromazine or intramuscular meprobamate (or both) for added effectiveness.[49] Some centers use paraldehyde, claiming that it also eliminates autonomic dysfunction.[54] Huge doses of all three agents combined will fail in very severe tetanus—as occurred recently at our hospital. This requires paralysis with tubocurarine or pancuronium. Succinylcholine may cause hyperkalemia in acute neuromuscular diseases and trauma states and should probably not be used. The paralytic agent is titered to achieve the desired effect of prevention of spasms as well as relief of muscle rigidity.[57] For humanitarian reasons, I usually sedate patients undergoing paralytic therapy or those who are paralyzed from their disease. Frequent verbal communication, reassurance and explanation of all care activities is very important to the patient in this remarkably stressful condition.

A checklist for respiratory care of paralyzed patients is presented in Table 5. Management of tracheostomy tubes is reviewed elsewhere,[51,53,59]

but several specific points will be emphasized here. Aspiration of oropharyngeal secretions past the tracheostomy tube cuff can be quite subtle and should be considered if a secretion problem, atelectasis or pneumonia develops. We check for an effective seal of the cuff against the tracheal wall by pharyngeal instillation of sterile water darkly dyed with sterile green food coloring followed by serial tracheal suctioning with careful observation for the green color. Recent experience with six chronically tracheostomized patients indicated that a pressure of 20 cm of water in the cuff (long, high compliant type) achieved minimal or no leak into the trachea, but only if the cuff was filled out far enough to eliminate creases as determined by proper ratio of tracheostomy tube to tracheal diameter.

TABLE 5.—*Checklist—Respiratory Care of Paralyzed Patient*

Airway Management
Prevent aspiration
  Assess cuff pressure
  Green water test
  Position for tube feedings

Prevent Tracheostomy Complications
Tracheostomy care
Humidification
Cuff: check volume and pressure
Cuff: adjust by pressure-volume curve
Cuff leaks:
  Check valve
  Increase inspiratory flow
  Increase tidal volume
  Increase FIO_2
  Saline into cuff
  Extra tracheostomy tubes at bedside

Ventilation
Criteria for ventilator support (weaning criteria)
Volume-cycled machine; automatic sighs
Alarms—low pressure: low volume; apnea
Monitor carbon dioxide pressure

Prevent Atelectasis
Sighs: automatic; manual
Repositioning
Prevent abdominal distention, pressure, ileus
Observe: vital signs, chest examination, x-ray studies of chest, alveolar-arterial oxygen gradient, compliance

Tracheobronchial Hygiene
FIO_2; humidity; tracheostomy care
Respiratory therapy equipment: maintain sterility, change frequently
Surveillance of tracheal flora and secretions
Repositioning: semiprone, proning
Chest physiotherapy
Suctioning; minilavage; fiberoptics
Drugs

Prevent Pulmonary Embolism

FIO_2 = fraction inspiratory oxygen

Before removing tracheostomy tubes from patients with neuromuscular limitations of swallowing and gag mechanisms, one should always assess the competency of these protective functions by use of the same colored water. With this technique, coupled with direct fiberoptic observation through the tracheotomy orifice, we have been able to differentiate aspiration due to subtle tracheoesophageal fistula from neuromuscular cause and aspiration through the vocal cords.

Additionally, the patient should be positioned with the head of the bed elevated during and after nasogastric tube feedings. Intestinal ileus is common in both botulism and tetanus and must be watched for, especially by gastric aspiration before each subsequent tube feeding.

Prevention of tracheal mucosa damage requires maintenance of high inspired humidity. Temperature alarm devices placed in-line near the connection of the respirator tubing to the tracheostomy tube are useful monitors since humidity is highly temperature-dependent.

The forerunner of tracheal perforation caused by the tracheostomy tube cuff is progressive tracheomegaly, which must be screened for by serial cuff volume measurement which is recorded on the ventilator flow sheet. At present it is axiomatic that high compliant cuffs of proper cylindrical shape be used exclusively. They are very safe with two provisos. First, inflation of the cuff must be limited to the low portion of the cuff's pressure-volume curve. With the tracheostomy tube in place in the trachea, this can be assessed easily with an anaeroid manometer and four-way valve. Second, and most important, the respiratory therapists must regularly measure the cuff pressure with the anaeroid manometer device. It is now widely recognized that filling the tracheostomy tube cuff empirically by just barely effecting a seal against the tracheal mucosa by listening for an airleak around the tracheostomy cuff results frequently in high enough cuff pressures to cause significant tracheal mucosal damage and even lead to perforation. Keeping the pressure at 20 cm of water during the inspiratory phase of ventilation in my experience has eliminated tracheomegaly and evident mucosal damage as observed by direct fiberoptic visualization. Utilizing these measures it is unnecessary to deflate tracheostomy tube cuffs of the type described and, furthermore, considerable past experience has shown that this measure was unsatisfactory. If tracheomegaly occurs, as indicated by increasing

cuff volume, one should recalibrate the pressure manometer, reassess the tracheostomy tube pressure-volume relationships as indicated above, and consider changing to a higher quality, more compliant cuff. Once tracheomegaly has begun, one may avoid perforation by changing the length of the tube so that the cuff impacts against a fresh portion of tracheal wall (you can modify endotracheal tubes for this purpose).

Since the trachea and esophagus are juxtaposed, it is important to use soft-walled and relatively small nasogastric or pyriformostomy feeding tubes as further prophylaxis against a tracheoesophageal fistula developing.

Nurses and respiratory therapists must be preinstructed to cope with the tracheostomy cuff leaks until personnel capable of changing such tubes arrive. The nurses must prepare for changing the tube by having all equipment ready and the patient properly positioned. Meanwhile, one should search for the leak in the valve of the external pilot balloon by clamping the tubing proximal to that valve. Despite a leaking cuff, ventilation can still be maintained usually by increasing inspiratory flow-rate and perhaps also inspiratory volume and ventilatory frequency. When these measures are insufficient, the cuff should be inflated with sterile saline which escapes slower than gas from the usual small hole in the cuff. Inspired oxygen concentration should be increased proportionate to the difficulty in maintaining adequate minute ventilation and to the degree of abnormality in oxygenation of the patient already present. Respiratory therapists and critical care nurses should also be preinstructed in methods of changing tracheostomy tubes (one size smaller for nonprofessionals) should the absolute necessity present itself. Two extra tracheostomy tubes are maintained at the patient's bedside.

Adequate alveolar ventilation is monitored by arterial carbon dioxide tension (or estimated by end-tidal carbon dioxide tension) and is best maintained by volume-cycle ventilators. In a paralyzed patient we use maximum alarm systems including inspiratory low pressure sensors and volume alarms on the expiratory circuit. Commercial alarm devices have been improved considerably. For example, one has a failsafe mechanism such that if its power line is disconnected from the wall outlet, a battery-driven alarm sounds. Additional apnea alarms (thoracic impedance or flow sensors) are useful during weaning from ventilator and later from tracheostomy or endotracheal tube support.

The same measurements used to indicate need for ventilator support are useful to predict and monitor safe weaning from the ventilator. Intermittent mandatory ventilation is well suited to weaning of neuromuscular patients.

Prevention of atelectasis in a paralyzed ventilator-dependent patient presents a major challenge. The problem is compounded by obesity and abdominal process including distention, pressure, pain or increased muscle tone. Normally, man sighs (increases alveolar volume and surface area to near-maximum levels) frequently, perhaps 5 to 15 times per hour. This rejuvenates the surfactant layer which is so remarkably effective at minimizing surface forces and preventing alveolar collapse. Only mechanical ventilators capable of automatically delivering deep sigh volumes should be used for a paralyzed or comatose patient. I am unaware of any widely accepted method of determining optimal sigh volumes for each patient. Many guidelines taught in respiratory therapy schools are definitely not based on sound physiological principles. In caring for patients with essentially normal lungs, I have extrapolated from normal human thoracic pressure-volume relationships and have adopted a pressure-based method as follows: inspiratory flow is set at a low level (such as 20 liters per min on the Bennett MA-1) and the sigh volume increased until an airway pressure of 40 to 45 cm of water is achieved (this is done intermittently over a period of time so as to avoid significant respiratory alkalemia). This flow setting was determined empirically to generate minimal flow resistance in the respirator and its tubing connected to tracheostomy and endotracheal tubes size 8.0 or larger. Unfortunately, most commercial ventilators have limited size volume capacity. You can easily create a larger volume manual sigh device from two or three resuscitation bags hooked-in parallel to an aneroid manometer. With this device it is easy to deliver sigh volumes with inspiratory hold for one second which probably increases the effectiveness. Similar systems have been described by others.[52]

Frequent repositioning of the patient constitutes a major part of the fight against atelectasis. Mechanisms involved are both the gravitational effects through lung interdependence and bronchial drainage of secretions. The paramount im-

portance of frequent repositioning cannot be overstressed and will be reiterated below.

Serial observations by physical examination, x-ray studies of the chest, alveolar to arterial oxygen gradient measurement or estimate (most sensitive) and static or dynamic compliance measurements (least sensitive) are best utilized all in combination to detect atelectasis. Tracheobronchial hygiene regimens also act to prevent atelectasis, bronchitis of excess degree, and pneumonia in these patients. I prefer the term hygiene because more than bronchial drainage is involved and, as a friend says, "You can keep the bronchial 'toilet' away from my airways." In tracheostomy patients bacterial colonization of the airways routinely develops, which usually is of relatively little consequence if pneumonia can be prevented. Careful tracheostomy care, attention to adequate humidity, effective sterilization of respiratory therapy equipment, frequent changing of ventilator tubing and humidifier contents, and so forth, with sterile techniques and minimizing inspired oxygen concentration contribute to prevention of pneumonia. Nevertheless, this complication remains the major lethal complication of neuromuscular respiratory failure.

Because nosocomial pneumonia constitutes a constant threat in ventilator patients, and the causative bacteria are usually treated best by knowing sensitivity data, and one must treat the usual Gram-negative pneumonia early as well as effectively, it is relevant to obtain deep tracheal samples serially for staining, culture and sensitivity testing. I usually assess the tracheobronchial flora in this matter every third day until a stable result is established or clinical events require reassessment.

The crucial role of patient repositioning has already been stressed. Attention to some specifics has proven necessary, however. The usual order of "turn patient hourly" is entirely insufficient if that is indeed all the nurses understand by it. They must be educated regarding the projectory of the segmental bronchi so they can visualize the necessity of turning the patient fully semiprone on one side to the opposite semiprone position,[53] especially to allow gravity to assist in drainage of the posterior segments. Horizontal and mild head-down positioning is also essential.

Recent experience has proven to me that even these positions are not sufficient. We instituted three times per day prone positioning ("proning") of neuromuscular respiratory failure patients utilizing firm 6-inch thick bolsters placed under the patient's forehead, upper chest and shoulders caudad to the tracheostomy tube, and along the lateral margins of the chest, abdomen and thighs. Despite the full side and semiprone turning at other times, and frequent suctioning, these patients produced copious secretions during the "proning" maneuver. In fact, we learned to be constantly ready to suction the tracheostomy and trachea during "proning" because of the occurrence of tracheal obstruction by these secretions. Undoubtedly these additional secretions emanate from the posterior segmental bronchi, which are ineffectively drained by traditional posturing. It is crucial to use firm, thick bolsters positioned to allow access to the tracheostomy for suctioning. The "proning" procedure allows the abdomen to fall by gravity, very likely increasing the end-expiratory lung volume at the lung bases and probably thereby helping to reverse atelectasis.

Chest physiotherapy, in conjunction with posturing for drainage, is probably more effective than posturing alone, and paralyzed but conscious patients usually relish the sensory input.

Suctioning techniques, especially sterile precautions, must be taught carefully to all members of the respiratory care team. Coudé tip catheters can assist in suctioning the left bronchial tree. Minilavage (5 to 15 ml of sterile saline solution) of the airways directed at specific locations of atelectasis and secretions can be very effective when combined with logical posturing just before and after instillation to gravity-assist the process. It is best to have a formal written protocol and thoroughly instruct therapists and nurses in this and other aspects of respiratory care through repeated in-service education programs.

The fiberoptic bronchoscope adds significantly to our armamentarium for reversal of secretion-caused atelectasis. Of course, drugs such as bronchodilators can be extremely beneficial for concomitant bronchial disease processes. Prophylactic antibiotics are in fact dangerous.

Pulmonary embolism is another major cause of death in paralyzed patients and especially in patients with tetanus.[57] Most centers routinely use prophylactic or therapeutic heparin regimens starting 24 hours after tracheostomy in such patients.

Finally, I would like to comment briefly on other aspects of care of paralyzed patients. Constant nursing and physician attention must be given to eye and mouth care, skin care and bowel

care, and there must be a total physical therapy program by therapists experienced with this type of patient. Septic complications of intravenous catheters must be prevented, and we try to avoid urethral catheters by using external drainage systems. Since gastric stress ulceration and bleeding is a significant cause of morbidity and mortality in tetanus and botulism, it is wise to institute prophylactic antacid therapy. Cimetidine may prove to be of additional value. A complete nutritional diet including vitamins, trace elements and minerals is necessary and fluids and electrolytes must be balanced meticulously.

The physician and nurses must be forewarned and prepared for autonomic dysfunction especially in cases of tetanus,[54,57,60] predominantly manifested as arrhythmias, tachycardia, labile blood pressure, hyperpyrexia, and excessive sweating and salivation.

Clostridia, in addition to the ability to cause neuromuscular disease noted above, also cause a spectrum of skin and soft tissue infections. The final segments of this symposium deal with these emergencies and the appropriate management of these syndromes.

Skin and Soft Tissue Infections

PHILLIP J. RAIMONDI, MD*

In addition to their etiologic roles in tetanus and botulism, clostridia are probably best known for their ability to cause myonecrosis or gas gangrene. It should be remembered, however, that this dramatic syndrome is uncommon and represents the far end of a broad spectrum of clostridial disease ranging from the benign to the fulminant and frequently lethal. In addition, clostridia are frequently harmless colonizers and therefore a culture report from any source showing clostridia must be interpreted in light of the clinical setting.[61,62]

Infections Other Than Gas Gangrene

Numerous clostridial species have been isolated from many different primary sites of infection (Table 6). Since these organisms are normal inhabitants of the human bowel, their presence in intraabdominal infection is not surprising.[63] The frequency with which they have been recovered is variable, however. Clostridia accounted for only eight of 198 (3.6 percent) anaerobic isolates in a group of patients with peritonitis or intraabdominal abscess studied by Lorber and Swenson.[64] On the other hand, in a similar group of patients with peritonitis or intraabdominal abscess reported by Finegold and associates clostridia were second in frequency only to bacteroides species and accounted for 43 of 173 (25 percent) anaerobic isolates.[65] Intraabdominal infection is typically polymicrobial and it should be noted that only rarely are clostridia isolated in pure culture.[65] The question then arises as to the importance of clostridia relative to the other organisms isolated in these infections. Certainly, overwhelming clostridial infection is an uncommon complication of intraabdominal sepsis suggesting that although clostridia may commonly be isolated along with other bacteria, they usually do not assume any special or unique importance. A similar statement can be made with regard to pelvic abscess. Clostridia may be present in such abscesses but subsequent severe clostridial sepsis is uncommon.[66]

TABLE 6.—*Clostridial Species Isolated from Human Infections*

Clostridium barayi	Clostridium limosum
Clostridium beijerinckii	Clostridium multifermentans
Clostridium bifermentans	Clostridium perfringens
Clostridium botulinum	Clostridium pseudotetanicum
Clostridium butyricum	Clostridium putrificum
Clostridium cadivaris	Clostridium ramosum
Clostridium capitovale	Clostridium septicum
Clostridium carnis	Clostridium sordelii
Clostridium difficile	Clostridium sphenoides
Clostridium fallax	Clostridium sporogenes
Clostridium ghoni	Clostridium subterminale
Clostridium hastiforme	Clostridium tertium
Clostridium innocuum	Clostridium tetani

Clostridial species, most notably C perfringens, have been isolated from the bile in as many as 19 percent to 20 percent of patients undergoing biliary tract surgical procedures.[67,68] Resulting clostridial sepsis or extensive soft tissue infection (or both) may develop in this setting, but fortunately are uncommon. A somewhat special circumstance may be so-called emphysematous cholecystitis. This is an uncommon form of acute cholecystitis characterized by the presence of gas in the gallbladder. Clostridia (usually C perfringens) are isolated in close to half of the cases.[67] In one series, gangrene or perforation of the gallbladder (or both) occurred in three fourths of the cases and the mortality rate was considerably higher than that of nonemphysema-

*Senior Fellow, Department of Medicine, VA Wadsworth Hospital Center and Division of Infectious Diseases, Harbor General Hospital.

tous cholecystitis.[67] Whether or not clostridia play a primary pathogenic role in this disease is an unsettled issue.

Clostridial organisms uncommonly cause pleuroplumonary infection. Bartlett and co-workers[69] and Lorber and Swenson[70] recovered clostridia from patients with aspiration pneumonia in only five of 54 (9 percent) and none of 47 cases, respectively. In none of Bartlett's cases were the clostridia in pure culture. Similarly, in cases of lung abscess and anaerobic empyema, clostridia are rarely isolated. Clostridial pneumonia and empyema have been reported following thoracotomy[71] and penetrating chest trauma.[72] Recently, Bayer and associates[73] reviewed C perfringens pneumonia and empyema. In seven of the 11 cases reviewed, the clostridial infection was preceded by an invasive chest procedure such as thoracentesis or chest tube insertion. It appears then that the pathogenesis of most pure clostridial pleuropulmonary infection involves introduction of organisms either by trauma or an invasive medical procedure.

Clostridia, either alone or in mixed culture, have rarely been isolated from a variety of other infections including osteomyelitis,[74] meningitis,[75] brain abscess,[76] subcutaneous abscesses[76] and spontaneous peritonitis.[77] Cellulitis can be caused by clostridia, usually C perfringens. This infection may complicate traumatic wounds and can coexist with clostridial myonecrosis.[77,79] Differentiation between the two diseases is important because of the need for more extensive surgical therapy in the latter disease.[78] Excessive gas formation with obvious crepitance is more common in cellulitis than in myonecrosis and may serve as a distinguishing feature.[79] Also, patients with clostridial cellulitis generally do not manifest the marked systemic toxicity characteristically seen in patients with myonecrosis.[79]

Gas Gangrene

The term gas gangrene refers specifically to clostridial myonecrosis. This disease was a major problem during the two world wars primarily because of inadequate early surgical management of traumatic wounds.[61] In civilian life, gangrene is still seen following trauma but it also occurs in patients with peripheral vascular disease, malignancy and a variety of intraabdominal disorders, and in obstetrical patients.

The organisms involved are the histotoxic strains of clostridia, so called because of their ability to produce exotoxins capable of tissue destruction. C perfringens has been the most common offender but C novyi, C septicum and several others can also cause gangrene (Table 7).[61] Of these, phospholipase C, or the so called alpha toxin, is felt to be the most important clinically, and is probably responsible for much of the tissue destruction seen in gas gangrene.[61]

TABLE 7.—*Histotoxic Clostridia*

Clostridium perfringens	Clostridium histolyticum
Clostridium novyi	Clostridium bifermentans
Clostridium septicum	Clostridium fallax

Intravascular hemolysis with spherocytes in the peripheral blood, intravascular coagulation and renal failure can be seen with severe clostridial infection.[61,80-82] The alpha toxin causes hemolysis in experimental animals[61] and has been proposed as the cause of hemolysis in man. Indeed, activity attributable to this substance has been identified in the blood of a patient with clostridial sepsis and hemolytic anemia.[83] Studies of the cell membranes from a patient with clostridia-induced hemolysis, however, showed major changes in the protein moiety, indicating that a factor other than phospholipase C may be of major importance.[84]

The cause of the intravascular coagulation has not been determined. Products of red cell destruction and damage to vascular endothelium by exotoxins have been proposed as inciting factors.[81]

The renal lesion is usually acute tubular necrosis and much less commonly cortical necrosis. A specific nephrotoxin has not been identified.

Gas gangrene secondary to trauma most frequently involves an extremity.[85] It may follow minor injuries[61] but usually develops in severe wounds with extensive muscle damage.[61,78] The vascular supply to the area may be impaired and the wounds are frequently contaminated by clothing, dirt or foreign bodies. Initial surgical management is often found to have been inadequate or delayed.[61,86] Such wounds provide an appropriate anaerobic environment for conversion of clostridial spores to vegetative forms and for growth of the vegetative forms. Exotoxins are produced, resulting in destruction of muscle. Variable amounts of gas may be produced and, in conjunction with edema fluid, result in increased local pressure and impairment of vascular supply and drainage. Further necrosis results,

creating additional areas appropriate for clostridial growth and the infection thereby spreads.

The period between time of injury and onset of symptoms ranges from hours to weeks but is usually a few days.[78,80] Severe pain is the earliest symptom followed shortly by tachycardia which, if present, is frequently out of proportion to what may be only low grade fever.[78] The primary wound is generally not pyogenic in appearance and the surrounding skin may initially appear normal or has been described as white, shiny and tense.[78] Crepitance is uncommon in early gangrene and may be minimal even in later stages. Excessive gas in tissues, in fact, should suggest another diagnosis such as clostridial cellulitis.[79,80] The wound itself may exude a watery brown discharge, the odor of which has been variably described as either sweet or foul.[78,79] This discharge typically contains red cells and clostridial organisms but very few polymorphonuclear leukocytes.[80,87] In the later stages, swelling in the area increases and the surrounding skin may become bronzed, deep burgundy, brown or even black in color. Large cutaneous vesicles develop, filled with serosanguinous fluid, again containing few polymorphonuclear leukocytes. This stage of the illness is characterized by severe systemic toxicity and possible hypotension. Renal failure may develop, as well as hemolytic anemia; however, the latter is more commonly seen with uterine infections rather than those following trauma.[61] Bacteremia is seemingly uncommon having been found in only 15 percent of cases by Caplan[85] and 13 percent of cases by Duff and associates.[88]

There may be diagnostic confusion between gas gangrene and a number of other soft tissue infections. These include clostridial cellulitis, streptococcal myositis and synergistic necrotizing cellulitis caused by an aerobic Gram-negative rod such as Klebsiella or E coli in combination with anaerobic streptococci or Bacteroides species.[78,79] Showing the presence of clostridia within a wound by Gram stain or culture does not establish the diagnosis of gas gangrene, however. Clostridia contaminate a high percentage of extensive traumatic wounds yet gangrene develops in very few.[78] Examination of muscle, therefore, is mandatory in order to make the proper diagnosis. Early in clostridial myonecrosis, the muscles are hemorrhagic and friable. Later, there is loss of contractibility, absence of bleeding from the cut surface and what has been described as a brick-red discoloration.[80] Gas may be grossly visible. Histologically, one sees edema, loss of normal muscle striations and eventual liquefactive necrosis of muscle. Clostridia are abundant within the necrotic muscle but there is minimal polymorphonuclear infiltration except at the periphery of the lesion.[90]

Patients with vascular insufficiency in whom gangrene develops are usually elderly and frequently have diabetes mellitus. A cutaneous ulcer may be present, but at times there is not an obvious primary lesion. Presumably, clostridia are introduced into the tissues by minor trauma and the ischemic environment permits proliferation. The pathogenesis is then similar to those cases precipitated by trauma.

Clostridial myonecrosis has also been reported as a postoperative complication of vascular surgical procedures or amputation of an ischemic extremity.[89,90]

There have been a number of reports of severe clostridial infection in patients with cancer.[91-97] The most common malignant lesions have been leukemia and gastrointestinal carcinoma, but patients with many other types of tumors have also been reported.[97] It has been postulated that the milieu within solid tumors is favorable to the growth of clostridia.[93,96] Indeed, as cited by Alpern and Dowell,[94] and Propst and Möse,[98] there have been instances of avirulent clostridia injected into patients with terminal malignancy. The organisms germinated only within tumor tissue resulting in liquefactive necrosis to tumor but not normal tissue.

A common finding in patients with cancer and clostridial infection has been disruption of the integrity of the intestines either by carcinoma, leukemic infiltrates or a nonneoplastic process. In patients with leukemia, clostridial bacteremia without extensive soft tissue infection has been most commonly reported but extensive myonecrosis can also occur.[94,97] This may involve primarily the bowel wall[93] or a distant area such as an extremity, usually without notable external trauma. Presumably, bacteremia arises from the bowel and a distant focus is seeded. Depressed host defenses, possibly coupled with minor focal trauma, permit proliferation of the clostridia and resulting gangrene.

Colon cancer is the most common gastrointestinal malignant condition complicated by clostridial infection. Such infections may develop with or without preceding perforation and abscess formation and can occur postoperatively follow-

ing resection of a carinoma. There may be bacteremia alone or extensive myonecrosis involving the retroperitoneal and anterior abdominal muscles. Extension into the thigh has been reported on several occasions.[95,99]

Gas gangrene is an uncommon complication of a number of intraabdominal disorders other than cancer. These include cholecystitis, penetrating duodenal ulcer, intestinal perforation, and perirectal or scrotal abscesses.[85,100-102] Gangrene has also been a complication of decubitus ulcers[103] and may follow many types of abdominal surgical operations including appendectomy, large or small bowel resection, gastrectomy, cholecystectomy and hemorroidectomy.[91,92,103] The muscles most commonly involved are those of the anterior abdominal wall and perineum. Occasionally, the retroperitoneum is involved and, rarely, the gangrene is localized to an extremity far removed from the site of the primary disease process or the operative wound.[101] The onset of illness is heralded by an abrupt worsening of the patient's condition. Either drowsiness or agitation may be the earliest changes with associated tachycardia, fever and later hypotension. Icterus due to intravascular hemolysis and deteriorating renal function are occasionally present. Increasing severe abdominal pain develops in some but not all cases. Tan or bluish discoloration of the skin overlying the area of myonecrosis has been described as the earliest local physical finding.[91] Crepitance may then develop but is often not pronounced. The process may spread quite rapidly and unless therapy is promptly instituted, will terminate in extensive myonecrosis, shock and death. ,

Clostridial infection in obstetrical patients is usually seen following abortion and fortunately is uncommon.[104] As pointed out by Smith,[81] these organisms may be present in the genital tract of 19 percent to 27 percent of aborting patients.[105,106] Eaton and Peterson,[108] however, found that clostridia were significant pathogens in only seven of 430 (1.7 percent) septic abortions. Once clostridia have been identified in the blood or genital tract, one is faced with the problem of distinguishing between colonization, benign transient disease and life-threatening infection. Ramsay, for example, reported about 28 patients with postabortal C perfringens bacteremia, 17 of whom had benign disease with minimal systemic toxicity.[104] Intrauterine clostridial infection may lead to typical features of sepsis, however, with fever, chills and hypotension. This disease clearly requires therapy and has been successfully treated with administration of penicillin and uterine evacuation.[107] The most devastating form of postabortal clostridial disease is myonecrosis or gangrene of the myometrium with so called "septicotoxemia." In its fullest proportions, this syndrome consists of the rapid development of pronounced systemic toxicity with brisk hemolysis, jaundice and hemoglobinuria, coagulation abnormalities, renal failure and shock. Lower abdominal pain and tenderness may be severe and gas within the uterine wall may be visible on x-ray films. The presence of severe hemolysis is considered a poor prognostic sign. Since the infection extends beyond the endometrium, simple uterine curettage is not considered adequate therapy for this condition.[108] Bilateral salpino-oophorectomy and hysterectomy appears to be the operation of choice and is probably the most important aspect of therapy.[107,108] Fluid replacement and blood transfusion are frequently necessary for shock and anemia. Penicillin in doses of 20 million units per day is the antibiotic of choice[6] with chloramphenicol being an alternative agent for penicillin-sensitive patients. Other treatment modalities such as heparin for intravascular coagulation, hyperbaric oxygen and clostridial antitoxin are of unproven value.[107,108]

Clostridial Bacteremia

A final note should be added about clostridial bacteremia. Clostridia may invade the blood from many if not all of the primary infections just reviewed. Even if histotoxic clostridia are involved, the clinical findings are quite variable. There may be little clinical evidence of septicemia as noted by Ramsay;[104] there may be shock indistinguishable from that caused by any other microorganisms; or, there may be fulminant septicotoxemia. The severity of the primary infection rather than bacteremia alone may be an important determinant of the clinical features. Although there are exceptions, most patients in whom severe hemolysis or coagulation abnormalities associated with clostridial bacteremia develop have an extensive underlying soft tissue infection. Furthermore, in the occasional patient with sterile blood cultures hemolysis may develop presumably from toxins liberated into the blood directly from the primary focus of infection.[104]

Another interesting aspect of clostridial bacteremia is that it may arise in seemingly unrelated

clinical settings. Alpern and Dowell,[109] for example, reported on patients with nonhistotoxic clostridial bacteremia whose underlying diseases included various pulmonary disorders, congestive heart failure, bleeding peptic ulcer, cirrhosis and iron deficiency anemia. The bacteremia was seemingly benign in some cases since ten of 12 patients who did not receive antibiotics survived. Gorbach and Thadepalli[76] also made this observation in their patients at Cook County Hospital. They were able to evaluate 29 patients with blood cultures positive for clostridia including some histotoxic strains. Whereas twelve of the 29 patients had soft tissue infections involving clostridia, a number of patients had underlying diseases not usually associated with clostridial infection. These include six patients with aspiration pneumonia, two with cavitary tuberculosis, two with a seizure disorder and one with meningococcemia. Why clostridial bacteremia should develop in these patients is an interesting but unanswered question.

Management of clostridial soft tissue infection is as varied as the infectious syndromes these agents may cause. Appropriate drainage of focal infection and administration of penicillin are the cornerstones of therapy. With more serious infection, aggressive therapeutic intervention is indicated.

Therapy of Clostridial Myonecrosis

ARTHUR A. SCHWARTZ, MD*

SUCCESSFUL THERAPY of patients with clostridial myonecrosis depends in great measure on the general state of health of the patient and the rapidity with which the diagnosis is made. Delay in the initiation of therapy may yield catastrophic results.[62]

Appropriate surgical management of clostridial myonecrosis includes several therapeutic modalities. While the relative importance of each of the following aspects of treatment remains a topic of controversy, many authorities agree that combinations of (1) surgical debridement, (2) antibiotic therapy, (3) hyperbaric oxygen and (4) supportive measures are necessary. The administration of polyvalent antitoxin has not been shown to be effective, and many centers have discontinued use of the antitoxin because of the risk of hypersensitivity phenomena.[110]

Surgical debridement is included by virtually all authors as a cornerstone of therapy. The time of operation and extent of debridement is less clear. Altemeier suggests wide, emergent debridement with multiple incisions and appropriate fasciotomies.[62] Roding and co-workers recommended limiting emergent surgical therapy to opening the original wound and incising abscesses.[111] These authors suggest delaying definitive surgical procedures until demarcation of necrosis occurs, with the hope of limiting disfigurement.[111] Early surgical intervention not only may allow decompression but also, as noted above, facilitates early diagnosis.

The role of antibiosis is somewhat less clear. The drug of choice is aqueous pencillin in doses of 20 million units per day. While the efficacy of penicillin is difficult to delineate, animal models have suggested the beneficial effect of antibiotics.[112] Second line drugs, to be used in patients allergic to penicillin, include cephalosporins, chloramphenicol and erythromycin. Sensitivity testing is advisable, especially if tetracycline, another macrolide, clindamycin or carbenicillin is being used.[111]

Hyperbaric oxygen has been shown to decrease mortality, and has been suggested to limit tissue necrosis. Positive results using hyperbaric oxygen have been obtained from several laboratories.[111-114] In an experimental study, Demello and co-workers showed the value of 100 percent oxygen at three atmospheres, but also showed that for maximum effectiveness in their model, debridement and antibiotics should be used.[112]

Supportive measures should include careful medical management as well as anticipation and prompt therapy of complications of clostridial bacteremia.

Management of these patients frequently involves volume expansion with intravenous fluid, plasma and blood. Shock is a frequent complication and rapid volume expansion may be necessary. Monitoring central venous pressure or (more reliably) pulmonary capillary wedge pressure may be of value in severely ill patients. The role of steroids remains somewhat controversial. Additionally, careful monitoring of the electrolytes and packed cell volume may avert potential com-

*Department of Surgery, Harbor General Hospital, Torrance, and Assistant Professor of Surgery, UCLA.

plications. Acute tubular necrosis is a not uncommon sequela of the shock and should be treated appropriately.

Hemolysis (especially in uterine myonecrosis) may be severe and require aggressive transfusion therapy.

Gas gangrene is a potentially preventable disease. Attention to good surgical principles is of primary importance with adequate debridement being the cornerstone of prevention. Antitoxin is ineffective as a prophylactic measure.

Summary

DAVID K. HENDERSON, MD: *The severity of all these syndromes depends in great measure on the potent toxins elaborated by these organisms. C botulism and C tetani produce neurotoxins while the histotoxic clostridia produce numerous toxins, most notaby phospholipase C, which are responsible for the extensive tissue destruction seen in the severe soft tissue infections.*

Specific antitoxins have been developed to counteract the effect of these toxins. These antitoxins, however, have met with limited success in the therapy of the clostridial-induced emergencies. Type B botulism antitoxin has been shown to be effective and hyperimmune antitetanus globulin is of value both in wound prophylaxis as well as in the therapy of tetanus. The efficacy of other antitoxins remains to be shown. Specific effective pharmacologic therapy for these syndromes, with the possible exception of guanidine in botulism, has yet to be developed.

Success in the management of each of these syndromes depends to a great extent upon rapid, accurate clinical diagnosis and the prompt initiation of both specific and nonspecific therapeutic measures. In the neuroparalytic syndromes, supportive care, particularly meticulous respiratory care, remains the cornerstone of therapy. Surgical debridement and drainage are of primary importance in the serious soft tissue infections.

Several areas of controversy remain to be clarified. The use of guanidine in botulism, the value of polyvalent antitoxin in myonecrosis and the use of antibiotics in all these syndromes are among those topics which need further study.

Each of these syndromes can be devastating and for that reason the clinician should maintain a high index of suspicion in the appropriate setting. Prompt diagnosis and therapy may prevent the development of a life-threatening toxic emergency.

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Refer to: Conservative management of rheumatoid arthritis—Medical Staff Conference—University of California, San Francisco. West J Med 129:121-125, Aug 1978

Conservative Management of Rheumatoid Arthritis

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and Robert C. Siegel, Associate Professor of Medicine and Orthopaedic Surgery, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *The topic for this morning's Grand Rounds is the management of rheumatoid arthritis. Dr. Kenneth H. Fye will lead the discussion.*

DR. FYE:† Today's presentation will be unusual for a Grand Rounds in that the emphasis will be clinical. Discourse on the latest laboratory efforts to define the etiology and pathogenesis of the disease will be assiduously avoided. I will present a general description of rheumatoid arthritis and then proceed to a discussion of that therapeutic discipline—physical therapy—that has traditionally (and perhaps symbolically) been relegated to the basement of virtually every medical institution with which I have had contact. I will end with a brief outline of the role that orthopedic surgical therapy plays in the care of patients with rheumatoid arthritis.

Rheumatoid arthritis is an autoimmune, systemic, inflammatory disease whose major, but by no means only, manifestations are articular.[1,2] The disease affects women of childbearing age with a sex ratio of 3:1. The arthritis is symmetrical, polyarticular, inflammatory and erosive; it typically involves the small joints of the hands and feet. Patients characteristically complain of morning stiffness, as well as pain and tenderness, of the involved joints. The classic deformities associated with rheumatoid arthritis are due largely to periarticular inflammation, which results in muscle spasm, atrophy, and laxity of periarticular supporting structures. The swan neck deformity (hyperextension of the proximal interphalangeal joint and hyperflexion of the distal interphalangeal joint), the boutonniere deformity (hyperflexion of the proximal interphalangeal joint and hyperextension of the distal interphalangeal joint), ulnar deviation and subluxation of the metacarpal phalangeal joints, and lysis of tendons are all due to soft tissue inflammation. Large joints, such as elbows, shoulders, knees and hips, can be involved in the inflammatory process, particularly late in the course of the disease. Cervical spine involvement, seen in 30 percent of patients, may lead to laxity of the transverse ligament. In such patients the odontoid process may impinge upon the spinal cord during flexion of the neck. Even though laxity of the transverse ligament may be seen on x-ray studies, one should consider surgical therapy (fusion of

*Lloyd H. Smith, Jr., MD, Professor and Chairman, Department of Medicine

†Kenneth H. Fye, MD, Assistant Clinical Professor of Medicine

the cervical spine) only in patients with a neurologic deficit secondary to the cervical spine defect.

The many extra-articular manifestations of rheumatoid arthritis are consistent with the systemic nature of the disorder. Constitutional findings, such as fever, chills, weight loss, lethargy and fatigue, reflect systemic inflammation. In 25 percent of patients, usually those with a positive rheumatoid factor and definite erosive arthritis, rheumatoid nodules will develop. Rarely, the manifestations of nodule formation may actually overshadow the arthritis. One of the commonest ocular expressions of rheumatoid disease, episcleritis, tends to be benign and does not require aggressive therapy. However, rheumatoid nodule formation on the sclerae should be treated vigorously, because scleronodular disease can lead to thinning (scleromalacia) and even perforation of the sclera.

Pulmonary disease is not rare in patients with rheumatoid arthritis. In 15 percent of patients there will be pleural disease—ranging from pleural nodulosis to nonspecific pleuritis with or without pleural fluid. Parenchymal findings, seen in 1 to 2 percent of patients, include diffuse interstitial lymphocytic infiltration, interstitial fibrosis, pulmonary nodular disease and infections—such as bronchitis, pneumonia or empyema. Caplan syndrome is an entity that has stirred a great deal of controversy in rheumatologic circles. It probably represents only the development of pulmonary rheumatoid nodules in patients with rheumatoid arthritis who happen to be miners with pneumoconiosis.

Vascular inflammation is a major component of rheumatoid disease.[3,4] The commonest form of vascular involvement is a bland, obliterative vasculitis involving small capillaries and venules. In 30 percent of patients with rheumatoid arthritis this form of vascular involvement is present; it is associated with a mild stocking-glove peripheral neuropathy. The lateral malleolar ulcers seen in 10 to 15 percent of patients with severe rheumatoid disease are due to vasculitic involvement of small cutaneous arterioles. In less than 1 percent of patients a systemic, necrotizing arteritis will develop that is clinically and histologically indistinguishable from periarteritis nodosa. Peripheral neuropathy is a frequent finding in patients with rheumatoid arthritis. Vasculitis may result in either a stocking-glove peripheral neuropathy or a mononeuritis multiplex, depending upon the severity of the vascular inflammatory process. In addition, synovial proliferation at various points in the body, such as the carpal tunnel, can lead to compression syndromes. As discussed above, in patients who have cervical spondylitis with laxity of the transverse ligament, one may see cervical myelopathy.

Cardiac involvement in rheumatoid disease is generally limited to the development of myocardial or epicardial nodules which cause nonspecific abnormalities seen on electrocardiograms.

Splenomegaly and leukopenia in a patient with rheumatoid arthritis is known as Felty syndrome.[5] Other clinical manifestations of Felty syndrome include lateral malleolar ulcers, rheumatoid nodule formation, lymphadenopathy, hepatosplenomegaly and recurrent infections.[5] These patients tend to have rheumatoid factors, antinuclear antibodies, thrombocytopenia and anemia, as well as leukopenia. Sjögren syndrome (keratoconjunctivitis sicca and xerostomia in patients with an autoimmune rheumatic disorder) is seen in 30 percent of patients with rheumatoid arthritis and must be considered in the differential diagnosis of any patient with rheumatoid disease in whom ocular complaints develop.[6]

Diagnosis

The diagnosis of rheumatoid arthritis rests primarily on the history and physical examination findings, but laboratory studies do offer clinicians valuable information. Patients with rheumatoid arthritis virtually always have an elevated erythrocyte sedimentation rate. Mild anemia, reflecting chronic inflammatory disease, is very common. Rheumatoid factors are seen in 75 percent and antinuclear antibodies in 20 percent of patients.[7] In individual patients one may see a variety of immunoglobulin abnormalities, including hypergammaglobulinemia or cryoglobulinemia. Radiologic evaluation may show soft tissue swelling, diffuse or periarticular osteoporosis, marginal erosions, ulnar deviation or subluxation of involved joints. Occasionally, biopsy confirmation of the presence of rheumatoid nodules in synovium or other involved tissues can be of diagnostic value.

Therapy

In rheumatoid arthritis as in every other disease, diagnostic evaluation is only a prelude to therapy. The treatment of rheumatoid arthritis must be directed both against the systemic and articular manifestations of the disorder. Treat-

ment of the systemic disease consists largely of pharmacologic control of specific manifestations.[8] Steroids or cytotoxic agents are used to treat rheumatoid vasculitis and nodulosis. Gold, penicillamine, lithium and splenectomy have all been advocated in the therapy of Felty syndrome. The patients with Sjögren syndrome are usually treated symptomatically, although in a rare patient administration of prednisone or cytotoxic drugs may be required. Treatment of the articular manifestations is intended to decrease pain and stiffness by controlling inflammation and to maintain or increase joint function by improving muscular strength, preserving articular motion, protecting joint stability and preventing deformity. Basically, there are three therapeutic modalities available to a clinician who is treating a patient with rheumatoid arthritis. In the remainder of this presentation I discuss the roles that physical therapy[9,10] and orthopedic surgical therapy[11] play in the treatment of a patient with rheumatoid arthritis. The third modality, pharmacologic control of inflammation, will not be discussed in this presentation.

Temperature manipulation

One of the keystones of physical therapy is the use of temperature manipulation. As a therapeutic modality, heat has antispasmodic, analgesic, and anti-inflammatory effects. The application of heat to an inflamed joint will increase the blood flow in and around articular tissues. Thermocouple studies have shown that the application of surface heat will decrease intra-articular temperatures and, therefore, interfere with the efficiency of the activated enzymes that mediate tissue inflammation. There are a variety of methods by which heat can be applied. Total body heat, applied simply with hot tubs or showers, is useful for the alleviation of morning stiffness and the facilitation of range of motion exercises of large joints, such as the hips. Heat can be applied to small joints by the use of hot water or paraffin baths. For larger joints, such as the shoulders or knees, hot packs are a convenient mode of heat application. Heat lamps can be used for large flat areas, such as the back, and are indicated when skin problems preclude the use of other forms of heat application.

Ultrasound has proved to be an effective way of applying deep heat without burning surface tissues, but ultrasound should be used only by experienced personnel; the improper use of this technique has been associated with significant complications. One must keep the crystal moving constantly to prevent deep tissue burns. Ultrasound should not be used in patients who have metallic implants or prosthetic devices because the metal can be heated to dangerously high temperatures. Because the metabolic demands of treated tissues will be increased, ultrasound should not be used over areas of vascular insufficiency. The brain and sense organs should not be exposed to ultrasound because of the possibility of heat coagulation. It is also recommended that ultrasound not be employed if there is a question of infection or malignancy because of the theoretical possibility of hematologic spread of pathologic factors following the microagitation that is associated with the use of ultrasound. Diathermy (ultra-high frequency radio waves of 2,450 megacycles) offers no significant benefits over ultrasound or more traditional methods of heat application.

The use of cold can also be of value in patients with rheumatoid arthritis. Hypothermia is particularly effective in the treatment of bursitis, tendinitis or acutely inflamed joints that are close to the skin surface. In these instances, cold packs may directly cool inflamed tissues and decrease the efficiency of inflammatory enzymes. In addition, cold does have an analgesic effect on nerve endings. There are problems with the use of cold therapy. Prolonged application of cold packs can lead to frostbite of the skin or muscle spasm. In addition, it is difficult to effectively cool deep-seated joints. Experience has shown that it is better to use temperature manipulation as a therapeutic modality for short periods (10 to 30 minutes) several times a day than for a long period of time once a day. Unfortunately, in young or working patients frequent application of temperature manipulation is often impractical.

Rest

A second aspect of physical therapy, and one that is commonly overlooked, is the appropriate use of rest. Patients with rheumatoid arthritis characteristically complain of severe fatigue in the early afternoon. Fatigue time, which is the interval between arising in the morning and the onset of severe fatigue in the afternoon, is so characteristic that it is traditionally used by rheumatologists as a measure of disease activity. Patients with active disease should be encouraged to take an afternoon nap when severe fatigue begins,

so they will be able to play a more active role in evening family life. In patients with an acute systemic flare admission to hospital and total bed rest may be called for, although bed rest should never be used without a concomitant program of appropriate exercise. Splints or braces are often valuable in "resting" individual joints. Static splints simply support an inflamed joint and protect susceptible articular and periarticular supporting structures from undue stress. It is hoped that such protection will prevent or inhibit the development of deformity. Static splints can either be used at night or in the daytime and can be made more or less rigid by the use of various splinting materials. Dynamic splints will support an inflamed joint but will still allow movement and exercise. They are of particular value in the preoperative and postoperative care of patients undergoing orthopedic surgical treatment. Chronic dynamic splinting can be used to restore lost function. An example would be the use of dynamic leg braces which would automatically extend the foot in patients who have foot drop due to either vasculitis with mononeuritis multiplex or to lysis of the posterior tibial tendon.

Exercise

Exercise is the third major aspect of physical therapy. The goals of an aggressive exercise program are to maintain or improve muscle strength, to prevent muscle contraction, and to prevent fibrous ankylosis of periarticular and articular supporting structures. Ultimately, it is hoped that if these goals are achieved, joint function will be maintained and deformity prevented. The specific type of exercise indicated in any individual patient depends upon the clinical situation. Passive range of motion exercises done by the therapist are indicated for acutely inflamed joints. Isometric exercises can be used to maintain strength when individual joints are too inflamed for significant motion.

In less acutely inflamed joints, assistive exercises—that is, exercises in which the therapist will help the patient move his own joints—are valuable. As the arthritis improves, active exercises—exercises done without the aid of a therapist—are useful in restoring muscle strength.

Finally, resistive exercises done against the resistance of the therapist or weights are indicated after the articular inflammation has been controlled.

Exercises, as with temperature manipulation, are most beneficial if done several times a day. The benefits of any therapeutic program in patients with rheumatoid arthritis are greatest if pharmacologic agents are used in conjunction with a solid physical therapy regimen. I have my patients take their anti-inflammatory drugs and then apply heat to affected joints for 10 to 30 minutes. Then, when the patient has received the combined anti-inflammatory, anti-spasmodic and analgesic effects of both the pharmacologic agent and the temperature manipulation, the patient will be better able to do his exercises effectively. The physician who treats patients with rheumatoid arthritis should be able to direct the physical therapy program. Prescriptions for exercises should indicate what type of exercise is to be done (passive, isometric and so on) and which muscles and joints are to be exercised. A trained therapist will know the specific exercise for each muscle group, so individual exercises do not have to be indicated.

Assistive Devices

Another aspect of physical therapy with which physicians should be acquainted is the use of assistive devices.[12] These devices aid a patient in accomplishing simple tasks that can become overwhelmingly difficult in the face of rheumatoid deformities. Feeding oneself, combing one's hair, brushing one's teeth, or going to the toilet can be frustrating experiences for patients with rheumatoid arthritis. Writing can become a monumental chore. Simply walking from one room to another can be a challenge. Fortunately, a variety of assistive devices, simple and complex, are available to aid debilitated patients accomplish the tasks of daily living.

Surgical Therapy

Orthopedic surgical procedures are an integral part of the long range treatment of rheumatoid arthritis. As in the other therapeutic modalities discussed, the goals of orthopedic surgical treatment are to decrease inflammation and pain; prevent or repair deformity; increase joint stability, and, ultimately, maintain or to increase joint function.

Some orthopedic procedures are largely prophylactic in nature; that is, they are intended to prevent deformity. Synovectomy is considered to

be a prophylactic measure because it results in the removal of the articular repository of the immune complexes that mediate inflammation. By the removal of this repository, and the removal of the invasive pannus, one hopes to decrease inflammation and to inhibit the destruction of articular tissues. Synovectomy is most successful in decreasing inflammation in those joints such as the knee where all the inflamed synovium can be visualized and removed. It is less successful as prophylactic procedure in those joints where it is impossible to remove all of the inflamed tissues, such as the small joints of the hands. In certain cases, arthrodesis, or fusion of the joint, is indicated to increase joint stability or decrease pain—or both. Arthrodesis is most useful in arthritis of the foot, wrist and thumbs.

Arthroplasty, or joint repair, often requires the use of joint prostheses. At present, effective prostheses are available for the hips, fingers and knees. New techniques are being developed that hold the promise of successful arthroplastic procedures in the elbows, shoulders, wrists and ankles. Orthopedic procedures can also be done to repair deformities due to loss of the integrity of periarticular supporting structures. Tendon repairs and the repair of both swan-neck and boutonniere deformities can be done in selected cases. Although rheumatologists are basically internists and constantly strive to avert the need for surgical intervention in their patients, they simply cannot ignore the fact that, in selected cases, orthopedic surgical therapy can be of inestimable value in the total care of patients with the systemic inflammatory disorder we know as rheumatoid arthritis.

Conclusions

There is a tendency for the average physician to become discouraged when treating severe, progressive rheumatoid arthritis. The disorder is chronic, the patients seem to have interminable complaints and the response of the disease to our therapeutic machinations is often painfully slow. However, the treatment of a patient with rheumatoid arthritis can be exceedingly rewarding. There is always something that we, as physicians, have to offer. Physical therapy, new anti-inflammatory agents, orthopedic surgical therapy, and our own optimism can always be used to buoy the flagging spirits of a beleaguered patient. Patients with rheumatoid arthritis tend to be young people who must face years, perhaps a lifetime, of pain and disability. They soon learn to recognize the shortcomings of medical science, but they are still tremendously grateful for what little we can do to help them.

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Important Advances in Clinical Medicine

Epitomes of Progress — General Surgery

The Scientific Board of the California Medical Association presents the following inventory of items of progress in general surgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in general surgery which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on General Surgery of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Chronic Visceral Ischemia

THE SYNDROME of chronic visceral ischemia has emerged as a uniform pattern of postprandial epigastric pain and weight loss distinct from other abdominal pain syndromes. Two mechanisms have been recognized. The less common of the two is compression of the celiac artery and occasionally the superior mesenteric artery as well by the median arcuate ligament of the diaphragm. The syndrome is largely limited to young women. Division of the ligament and instrumental dilatation of the residual celiac stenosis has provided dramatic and durable relief of pain in 62 of 68 patients operated upon at the University of California, San Francisco.

The other mechanism is multiple visceral artery occlusions by atherosclerosis. The traditional technique for surgical management has been the utilization of bypass grafts extended in a retrograde fashion from a more distal portion of the aorta to a patent segment of the involved artery beyond the site of disease. These have been accompanied by a high frequency of early or late failure. In order to improve these results, variations of the original grafting techniques and endarterectomy have been tested during the last eight years at the University of California, San Francisco, and the results evaluated by late aortography. An unanticipated finding was the predominance of females in the series and the frequency of a form of atherosclerosis in the ab-

dominal aorta in which the intima became a soft, thickened and homogeneous layer which virtually overflowed the visceral and often the renal arteries as well. Thirty-eight patients have been operated upon. The conclusions from this experience were as follows:

- Grafts placed in an antegrade fashion and originating from the generally undiseased distal thoracic aorta (transabdominal approach) are hemodynamically more sound, and easy to apply.
- When both the celiac and superior mesenteric arteries are involved, grafts to the celiac alone will generally suffice to revascularize the distal branches of both arteries and relieve symptoms.
- Late failure is a function of the graft material. Long-term patency of Dacron® grafts was 6/6, arterial autographs 3/3 and saphenous vein grafts 1/6. Saphenous vein grafts are no longer used.
- Endarterectomy is an effective method for a more complete operation. When done through a thoraco-retroperitoneal abdominal approach and a trapdoor aortotomy, removal of a sleeve of aortic intima produces a specimen that includes the orifice lesions in the visceral arteries and the renal arteries also if they are involved. This approach facilitated coincident aorta-iliac reconstruction which was indicated in eight patients.

EDWIN J. WYLIE, MD

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Atheroembolism

ALTHOUGH THE MAJORITY of thromboemboli are cardiac in origin, detachment of loose atheromatous aggregates from a major artery may be another serious yet correctable source of embolization. Though atheroembolism was first recognized in 1862, its importance has not been appreciated until recently. Dissemination of grumous material from ulcerated plaques at the carotid bifurcation is now well established as a cause of transient ischemic attacks or stroke and carotid endarterectomy for the condition is being done with increasing frequency.

Cases of atheroemboli to the abdominal viscera including the kidneys, pancreas, stomach or bowel have been recorded in the literature, but as yet surgical remedial measures in such cases are rarely attempted.

The symptoms of atheroemboli to the lower extremities are often insidious and may at times elude the most astute diagnostician. Myalgia, aching and cramps, often intermittent in nature, may be the first symptoms. Eventually, gangrene of the toes develops despite the presence of ankle pulses. Successful management of patients involves clinical awareness of the entity followed by angiographic confirmation and prompt endarterectomy or graft replacement of the diseased aorta. Arteriograms typically show ulcerated disease or plaquing of the aorta with sharp angiographic blockage of digital vessels. Atheroembolism may also be seen in the upper extremity but with less frequency.

JACK H. M. KWAAN, MD
JOHN E. CONNOLLY, MD

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Management of Hepatic Trauma

MAJOR ADVANCES in safety of hepatic resection have been based upon new technical, anatomical and metabolic knowledge. Nevertheless, mortality has remained high when injuries have been associated with major vascular injury and when hepatic lobectomy has been required. The additive effects of lobectomy, a formidable procedure, upon existing preoperative and operative hypovolemia, hypotension and associated injuries, have often resulted in death.

There has been renewed interest in resections of lesser magnitude but adequate to debride damaged liver and to control bleeding. Even extensive lacerations and explosive injuries caused by abrupt deceleration can often be successfully managed by the piecemeal removal of devitalized hepatic fragments and careful ligation of vessels and ducts, followed by adequate drainage.

Rapid fluid resuscitation and complete evaluation should be followed by prompt surgical exploration of the abdomen with early extension of the incision into the chest by partial splitting of the sternum, if necessary, to provide sufficient exposure of bleeding sites and to control them.

Initial packing often controls bleeding temporarily for orderly assessment of the location and extent of bleeding. Fortunately, most liver injuries are minor and respond to simple suture methods and adequate drainage.

Clamping of the portal triad (Pringle maneuver), isolation of the intrapericardial or abdominal vena cava, subdiaphragmatic aortic clamping and intracaval shunts are methods sometimes useful in gaining temporary hemostasis. Under certain conditions even prolonged packing with subsequent removal has been useful in the surgical armamentarium.

The place of hepatic artery ligation for the control of hemorrhage has not been settled. In Mays' experience, hepatic artery ligation has been uniformly well tolerated. Others report recurrent bleeding and hepatic dysfunction after its use. In selected patients, ligation should be given careful consideration as an alternative to major hepatic lobectomy.

In these cases careful supportive postoperative management directed to the prevention of multiple organ failure is required. DON R. MILLER, MD

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Peritoneoscopy in Gastrointestinal Surgical Operation

PERITONEOSCOPY is being rediscovered by surgical gastroenterologists. Although widely used in Europe, and in this country by gynecologists, peritoneoscopy (laparoscopy) in gastrointestinal surgery is not widely appreciated.

Laparoscopy is the endoscopic examination of the peritoneal cavity and its contents after the induction of pneumoperitoneum. By visualization, indirect palpation and tissue biopsy studies, open laparotomy can be avoided in approximately 50 percent of patients for whom an operation has been indicated because of obscure diagnosis or possible intraabdominal trauma.

The potential application and benefits of peritoneoscopy are immediately apparent to practicing clinicians. These include elderly debilitated patients with suspected carcinomatosis; patients with fever of unknown origin, intraabdominal masses or jaundice of cryptic origin, and trauma victims with equivocal signs of intraabdominal injury—to name only a few.

Gastrointestinal surgeons have sometimes been reluctant to accept new modalities for diagnosis and treatment. In many ways this is a laudable posture at a time when the proliferation of new tests and therapies is escalating the cost of health care delivery without documented benefit to patients. In the experience of this author, however, peritoneoscopy can avoid many costly indirect diagnostic examinations and potentially hazardous operations in eldery and high-risk patients.

Competence in peritoneoscopy is now a part of the better training programs in gastrointestinal surgery. Practicing clinicians may wish to acquire training in these skills to explore their potential in their practices. L. DENBESTEN, MD

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The Continent Kock Ileostomy

THE CONTINENT INTERNAL ILEOSTOMY POUCH which was introduced in 1969 by Professor Kock is an evolutionary descendant of ileocystoplastics, done by Goodwin. It is best applied in patients with true mucosal ulcerative colitis. A patient with Crohn disease who has already had an ileostomy and has shown no recurrence of the disease over the period of many years, rarely becomes a candidate for the pouch. The pouch may be created as a secondary operation or as a primary operation. To form such a pouch at the time of the original ileostomy and colectomy adds at least another hour to the operative time. A depleted patient may have healing difficulty with the complex suture lines. In 60 percent of patients with colitis, the ultimate pathological diagnosis is Crohn disease. Since roughly half of these patients were diagnosed initially as having mucosal colitis, it is incumbent upon the surgeon to be absolutely certain that he is not operating on a patient with undiagnosed and untreated Crohn disease. Treatment of a recurrence of the disease in the pouch may cost the patient unnecessary bowel loss if fistulas and other complications ensue.

The success of operation depends on the accurate placement of permanent sutures through both layers of the retroverted nipple as close to the mesentery as possible in order to prevent reduction of the nipple. Damage to the mesentery may result in ischemia of the ileum distal to this point or serious intramural hematoma. Placement of sutures too far from the mesentery may result in reduction of the nipple with concomitant incontinence and an inability to drain the pouch by catheter.

The Kock pouch is a great advance in the management of colitis. It must be applied, however, to a very carefully selected group of patients and should be done only by surgeons who truly understand the spatial relationships of the mesentery of the pouch and the nipple.

WILEY F. BARKER, MD

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Current Approaches to Evaluating Carotid Disease

ANGIOGRAPHY, the original and ultimate diagnostic technique, provides the most accurate anatomical assessment of carotid lesions. The refinements of multiple views, selective catheterization and subtraction films have greatly improved quality and reliability. However angiography is not suitable for screening or repeated follow-up.

Four different noninvasive approaches have been developed: (1) Oculopneumoplethysmography (Gee method) measures ophthalmic artery pressure indirectly. Suction applied to small scleral cups increases intraocular pressure; the systolic endpoints are detected by transducers coupled to each cup. Information concerning collaterals can be obtained using carotid compression. (2) Recording of systolic pulse arrival times at the eyes and the earlobes has been described by Kartchner, who has correlated pulse delay with significant stenosis. (3) A significant internal carotid stenosis produces decrease or reversal of ophthalmic artery flow. This can be evaluated by studying changes in flow patterns in the supraorbital or frontal arteries produced by compression of the superficial temporal or other external carotid branches. Present techniques employ a Doppler ultrasound flow meter or a photoelectric cell. (4) Two dimensional images of the carotid bifurcation can be recorded by ultrasound techniques, but at present resolution is not comparable to contrast angiography.

The first three noninvasive techniques can provide high accuracy in detecting significant stenosis (more than 50 percent reduction of lumen diameter), but are of no value with moderate lesions which may be sources of emboli. The imaging devices can show small lesions but at present do not have the resolution to identify ulceration reliably.

Angiography provides an accurate anatomic rendition of carotid lesions and should be done on all patients considered for surgical operation. Noninvasive techniques can provide additional information on the hemodynamic abnormalities. Unlike angiography, the noninvasive tests are particularly well-suited for screening, for evaluating asymptomatic bruits and for postoperative follow-up studies. With improving technology, the new approaches will have increasingly important roles in evaluation of cerebrovascular disease.

J. DENNIS BAKER, MD

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Surgical Management of Gastroesophageal Reflux in Infants and Children

IN CONTRAST to the general view that infantile chalasia is a benign, self-limited condition, gastroesophageal reflux has been recognized with increasing frequency as a pernicious cause of malnutrition, growth retardation, recurrent aspiration, esophagitis and stricture, occasional asthmatic attacks, and other previously unexplained conditions in infants and young children.

The condition is particularly common in children with neurologic disorders and has been

recognized with increasing frequency in children following repair of esophageal atresia. Nocturnal reflux is particularly insidious and may precipitate an acute coughing episode in a sleeping child. Recent application of more precise diagnostic studies to the evaluation of reflux has made it possible to identify symptomatic children more easily. Whereas the findings on cine-esophagrams may not always correlate with the clinically symptomatic child, measurement of esophageal pH after abdominal compression (Tuttle test), measurement of lower esophageal sphincter pressure and esophagoscopy with biopsy, provide a more complete physiologic evaluation of gastroesophageal reflux. The inability to do many of these studies in young children without heavy sedation or general anesthesia and the lack of studies which indicate normal values has made the interpretation of specific values difficult; however, comparison with data obtained from other patients in the same laboratory and studies from patients who have undergone surgical repair of reflux have provided guidelines.

Gastroesophageal fundoplication has been used effectively to prevent further reflux in a large number of symptomatic children with low morbidity and less than 1 percent mortality. Concomitant temporary gastrostomy prevents the gas bloat syndrome, assists in postoperative feeding and serves as a partial gastropexy. Further application of fundolplication for the management of symptomatic infants and young children with gastroesophageal reflux appears justified.

ERIC W. FONKALSRUD, MD

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Shock: Rapid Transfusion, Calcium Levels, pH and Body Temperature

THERE ARE MANY circumstances today in which rapid transfusion of blood is critical in resuscitation, and yet all surgeons are familiar with patients who have just received a large amount of blood and, in spite of this, suffer acute myocardial depression and death by way of the mechanism of anoxia and arrest.

It has been shown both experimentally and clinically that rapid transfusion (that is, at a rate exceeding 1 ml of blood per kg of body weight per minute) of citrate-phosphate-dextrose (CPD) blood reduces ionized calcium in the arterial blood immediately following the infusion, which in turn causes decreased myocardial function, as documented by Starling function curves (stroke work versus filling pressure). This dangerous myocardial depression can be prevented by the simultaneous administration through a separate central venous line of calcium chloride at the rate of 1 mg per ml of CPD blood administered.

This same phenomenon of myocardial depression may occur if a patient receiving hemodialysis is suddenly subjected to a large load of dialysate low in ionized calcium.

In many of the situations in which this myocardial depression occurs, the patient in need of the transfusion is apt to be hypothermic, as well as acidotic, and if the flood which is administered is itself acidotic and cold, the transfusion may aggravate these conditions.

What is the correct serum pH for optimal myocardial function during hypothermia? The answer to this question is derived from observations by comparative physiologists. Cold-blooded animals maintain normal myocardial function during hypothermia in contrast to man. The cold blooded animals hyperventilate and become alkalotic at low body temperatures, developing, for instance a pH of 7.70 at 28°C. In experimental animals, myocardial function was measured at a body temperature of 28°C and at a pH of 7.40. A significant depression was observed which was largely relieved by rendering the animals alkalotic.

These observations only confirm the importance of making the hypothermic patient in shock normothermic, treating acidosis vigorously while the patient is hypothermic, and further reducing the risk of additional myocardial depression by the simultaneous administration of ionized calcium when large amounts of CPD blood are administered rapidly. These precautions may avoid the sudden collapse of the patient who otherwise seems to have been properly treated.

DOUGLAS McCONNELL, MD

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The Role of Paracentesis and Lavage in the Evaluation of Penetrating Torso Injuries

BECAUSE OF CONTINUED ADVANCES in surgical care, mandatory celiotomy has become the widely acceptable method of management for penetrating injuries of the torso. Utilizing this method, less than 5 percent of all stab wounds and only 10 percent to 15 percent of gunshot wounds of the abdomen are now lethal. As a result of this more aggressive surgical approach, a new problem, negative celiotomy, has occurred. Penetrating abdominal wounds without associated visceral injury have been reported in as many as 53 percent of all penetrating torso injuries managed under a policy of immediate mandatory exploration. Since negative celiotomy is associated with a significant mortality rate, postoperative morbidity and sizable cost, paracentesis and lavage are widely accepted as a valuable adjunct in the evaluation of these patients.

A satisfactory protocol using paracentesis and lavage for the evaluation of penetrating torso injuries is as follows:

- Immediate celiotomy is carried out in the presence of (1) evisceration, (2) distended or distending abdomen, (3) deteriorating vital signs, (4) roentgenographic demonstration of free air in the peritoneal cavity.
- If the above gives negative findings, paracentesis is done with a Trocath® placed through a stab wound just below the umbilicus. The technique is similar to that reported by Olsen. If blood is obtained (20 ml or more), celiotomy is carried out. If less than 20 ml of blood is present, the peritoneal cavity is lavaged with saline or lactated Ringer's solution, approximately 20 ml per kg of body weight to a maximum of 1,000 ml. Lavage is considered positive and celiotomy done if newsprint cannot be read through the intravenous tubing.
- If paracentesis and lavage results are negative, patients are observed in the hospital. No patient is observed unless paracentesis and lavage have been done.
- All gunshot wounds of the torso are initially evaluated in the operating room as to extent and depth. When injuries are suspected to be superficial and there are no clinical indications for immediate celiotomy, paracentesis and lavage are done.

The above policy has resulted in lowering the negative celiotomy rate to approximately 8 percent.

EARL F. WOLFMAN, JR., MD

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Fiberoptic Colonoscopy

FIBEROPTIC COLONOSCOPY has gained acceptance as a valuable adjunct in the diagnosis and treatment of colonic diseases. Current instruments are technologic marvels that permit inspection, photography biopsy, lavage, polypectomy and retrieval of foreign bodies. Colonoscopy is no longer the province of a few pioneers; it is widely applied in the community. Several questions remain, however, about the indications for colonoscopy and the hazards of the procedure.

Broadly stated, colonoscopy should be done if colonic symptoms, signs or radiographic abnormalities need further clarification. Unexplained diarrhea, occult blood in the stool and equivocal findings on barium studies are among the valid indications for colonoscopy. On the other hand, should colonoscopy be done in patients with irritable colon syndrome, chronic constipation or vague chronic abdominal pain? The yield of organic disease in these patients is so low that colonoscopy for such slim indications probably is not justified.

The role of colonoscopy in the diagnosis and treatment of colonic neoplasms has not been clarified fully. Is every tiny radiolucent defect an indication for colonoscopy? Should colonoscopy be done in a patient with a rectal polyp but normal findings on barium enema? Should colonoscopy be done routinely at arbitrary intervals after neoplasms are removed endoscopically or surgically, or should it be done only if some other screening test result is abnormal? If so, which other test should be relied upon and at what intervals should it be done?

The morbidity of colonoscopy is reportedly 0.34 percent to 0.42 percent for diagnostic procedures and 1 percent to 2.32 percent for polypectomies. These complication rates were compiled by a relatively small number of colon-

oscopists who were interested in establishing the safety of the technique. Now that colonoscopy is being done by physicians and surgeons of varying interest, skill and experience, will the morbidity—and mortality—remain at acceptable levels?

These questions and many others must be answered before the proper place of this important advance is known. Colonoscopy is expensive, and it carries definite risks. For the present is seems wise to limit use of the procedure to patients who have solid indications.

THEODORE R. SCHROCK, MD

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EDITORIALS

Medical Ethics and Contemporary Needs

THE HOUSE OF DELEGATES of the American Medical Association decided wisely when it did not accept the revision of the Principles of Medical Ethics proposed by the Judicial Council at the recent AMA session in St. Louis. It is not that these were bad ethics or that medical ethics are no longer needed. Rather the principles, as stated, simply do not meet contemporary needs. It is time they were reassessed in terms of what is now needed to guide physicians in practice and to guide the profession as a whole.

Historically professional ethics have set the approved standards for professional behavior. In medicine they have also served to separate "ethical physicians" and the "ethical profession" from others who did not meet these standards, or perhaps had other standards. The implication, however, was that there was something better about having an ethical physician and an ethical profession, and no doubt this was true. The Code of Ethics established by the American Medical Association more than 100 years ago, and since occasionally modified, served well for the times and laid the groundwork for the development of medicine as an influential force in American society, as it remains today.

Many years ago the late Chauncey Leake stated, in a reprinting of *Percival's Medical Ethics,*[1] "A profession has for its prime object the service it can render to humanity." This is the sole justification for the special societal status that has been given to medicine and certain other professions. Codes of professional ethics have been an important means of preserving such special status. To accomplish this for medicine as we find it today, it appears that medical ethics should provide some protection for the interests of patients, of the public, and indeed for the profession itself, because it is obviously in the interests of both patients and the public that they be served by a strong, well-qualified medical profession. These points are all addressed to some extent in the current Principles of Medical Ethics but with very little specificity.

It can be argued, and it has been argued, that in the long run the medical profession will prosper so long as patients and the public are well served. This is probably true in the generality, but in contemporary society there are some inherent conflicts which deserve attention. For example, at what point does the interest of the profession become self-aggrandizement—something beyond the service it can render to patients and the public? And what about the as yet ill-defined responsibilities of patients and the public (including government) in medical and health care, and how should the responsibilities of physicians be defined in relation to these? In some instances the ethical responsibilities and duties of physicians are clear and in others they are not. For instance, while it is clearly unethical and probably illegal for a physician to abandon a patient, is it unethical or illegal for physicians to strike or withhold their professional services? And, if so, where is the distinction? The interests of physicians, patients and the public are not always the same, yet each has responsibilities to each of the others. These require more study in terms of contemporary relationships. In addition medicine has a special responsibility to develop and apply its knowledge and expertise to help patients and the public achieve better health, well-being and quality of life. These kinds of professional responsibilities should have better recog-

nition and better definition in any statement of principles or code of medical ethics to be adopted by the profession at this time.

But beyond this a growing number of genuine ethical dilemmas are beginning to confront physicians in practice. These are largely an outgrowth of recent scientific and technologic progress and the social, economic and political reactions to this progress. These ethical dilemmas generally reflect conflicts among and between the realities of human biology and a variety of social, economic and political interests. For example, there are ethical problems around when a human life begins, or when it begins to be human, and also around when death occurs. Ethical problems arise for a physician when a responsibility for the interests of society conflicts with what he deems to be best for a particular patient or what he himself holds to be right. And to what extent is an ethical physician responsible for costs in patient care and how is this responsibility to be fulfilled? And what are the ethics of a physician's political involvement as a professional, or as a citizen who happens to have professional knowledge and expertise? And what about the stance and responsibility of an ethical physican in the face of sometimes arbitrary, bureaucratic, government regulations which may simply not make sense in a given situation? Many other examples could be cited.

This is a time of fundamental reassessment of the relationships of physicians with other health professionals, of physicians with patients, and of the medical profession with the society it serves. Ethical questions of many kinds are at issue. Just as was the case more than 100 years ago, the medical profession in America needs a contemporary code of ethics to define its role and responsibilities as a profession whose prime object still is the service it can render to humanity. Leadership in this area is essential if medicine is to continue to be the effective force in American society that it has been. It is likely that a broadly based study of medical ethics in all of its modern dimensions will be needed, whether under the AMA Judicial Council or other auspices. Once again we call upon the American Medical Association to affirm its leadership by causing such a needed and potentially far-reaching study to be done. Time is running short.

—MSMW

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The Clostridial Syndromes

Not too many years ago, a discussion of anaerobic bacteria important in human disease would have focused almost exclusively on the clostridial species. In the past decade or so, however, dedicated investigators, improved bacteriologic techniques and intense educational programs have called attention appropriately to the importance of other more common anaerobic infections. As so often happens in this situation, the old is relatively forgotten in the blush of enthusiasm for the new.

Interest in the clostridia has been sustained, however, because the diseases they produce are important, and bacteriologically they are fascinating organisms. Elsewhere in this issue, a Specialty Conference by Henderson and colleagues emphasizes the clinical diversity and challenges of the clostridial syndromes. These include botulism, tetanus and infections caused by the histotoxic clostridia. Faced with a spectrum of clinical problems ranging from potentially lethal food poisoning to gas gangrene, it may be helpful to concentrate briefly on the unifying features of these syndromes which justify considering them together.

To begin with, the clostridia are strict anaerobes widely distributed in an environment rich in oxygen. Survival depends on their ability to form spores that are remarkably resistant to inimical surroundings. With some species variation in distribution, these spores are found in soil, house dust and the feces of a variety of animals including humans. Fortunately, of the multitude of species within the genus Clostridia, only a small number have importance as potential pathogens in humans. Even so, all of us live in an environment heavily contaminated by organisms that have awesome disease-producing capability.

This ubiquity and lethal potential contribute to the fascination of these organisms, because even in primitive surroundings, diseases caused by clostridia are relatively uncommon or rare. For example, during the Penisular War in Spain from 1808 to 1814, British soldiers contracted tetanus at a rate of 12.5 cases per 1,000 wounded.[1] Considering the massive contamination of wounds that must have occurred and the scientific ignorance and primitive surgical practices of the times, that rate is surprisingly low. In the case of botulism, less than 2,000 cases have been reported in the United States since Van

Ermengem first isolated the causative agent in 1895. Even allowing for the extensive underreporting and failure of recognition implicit in these data, botulism must be considered a rare disease.

The key to this apparent incongruity lies in the fact that the pathogenicity of the clostridia and the manifestations of diseases they produce are due almost entirely to exotoxins they elaborate. For example, botulinus toxin is solely responsible for the neuroparalytic syndrome referred to as botulism, and tetanospasmin is the mediator of the characteristic muscle spasms of tetanus. Producing diametrical effects, these polypeptide neurotoxins are among the most potent biological poisons known to man with lethal doses estimated in numbers of molecules rather than micrograms. Fortunately, not all of the toxins produced by clostridia are as potent or have the same clinical importance as these. A number of species produce toxins that are lethal to experimental animals but of no consequence to humans, and many of the human pathogens produce an array of toxins with minimal or no recognizable influence on the syndromes produced.

Another major factor contributing to the relative rarity of most costridial syndromes is that toxin production depends upon germination of spores and growth of the resulting vegetative cells. While a variety of conditions influence this process, an absolute requirement for clostridial spores to germinate is a very low reduction-oxidation potential. In classical botulism, these conditions develop when certain foods are improperly preserved and prepared. Disease occurs when the toxin is ingested and absorbed from the gastrointestinal tract. However, botulinus toxin is so potent, illness can follow absorption from skin with minor disruptions in integrity of mucous membranes.

Recent recognition of infant botulism emphasizes the importance of learning more about factors influencing germination. This syndrome has been recognized only in the past two years. It occurs in infants up to six months of age, and surprisingly no source of ingestible preformed toxin has been identified in any of the 58 cases identified through early 1978.[2] Apparently these children ingest spores which then germinate and produce toxin in the lumen of the gut. Presumably this phenomenon does not occur in adults, but we should recognize that much of what we do to patients in the course of treating other diseases could alter factors that normally inhibit germination in the intestinal tract. Investigation might show that this process accounts for unexplained weakness in some adults with chronic or debilitating illnesses.

In the case of tetanus and the rare entity of wound botulism, toxin is produced in tissues where organisms have been introduced by trauma and conditions develop which allow them to germinate and grow. The latter is a critical requirement that is infrequently met. Data show that contamination of wounds by Clostridium tetani spores is common, yet tetanus is relatively rare. This fortunate discrepancy occurs, at least in part, because of good wound care which minimizes factors such as vascular injury, necrotic tissue, foreign bodies and infection that can facilitate development of anaerobic conditions in tissues.

Histotoxic clostridia, the most important of which is Clostridium perfringens, differ significantly from other species. They produce proteolytic enzymes in addition to multiple toxins. This combination confers upon them the capability of causing a wide variety of clinical entities. The counterpart of the toxin-mediated syndromes of other clostridia is myonecrosis (gas gangrene). All of its local and systemic manifestations can be produced experimentally by intramuscular injection of a lecithinase called the alpha toxin. The role of this lecithinase and less potent toxins in the pathogenesis of other clinical entities caused by these organisms is variable. For example, in postabortal sepsis, hemolysis is often severe while bacteremia associated with biliary tract infections or cryptic abscess may be quite routine. Clostridial cellulitis is associated with excessive gas production and local proteolysis, yet it frequently is referred to as benign because myonecrosis is absent. Many factors influencing the production and action of toxins are not well understood. However, they are becoming critically important, because spontaneous infections caused by Clostridium perfringens and Clostridium septicum are being recognized with increasing frequency in patients with malignancy and other diseases.

It is not widely recognized that C perfringens is one of the commonest causes of bacterial food poisoning in man.[3] Profuse watery diarrhea and mild abdominal cramps follow ingestion of food heavily contaminated with vegetative forms that then sporulate in the intestinal lumen and release

an enterotoxin. This enterotoxin, which is biologically very similar to that of Vibrio cholerae and Escherichia coli, has not been shown in vegetative cells. So far, this mechanism of producing illness is unique among the clostridia, and adds to their fascination.

From the perspective provided by this overview, the discussion of the costridial syndromes by Henderson and his colleagues may be appreciated more fully. They have provided accurate, well referenced details about bacteriology, pathogenesis, clinical presentation, differential diagnosis and treatment of these diseases. Their inclusion of a practical section on respiratory care in tetanus and botulism is quite useful. One of the fortunate characteristics of the potent toxins responsible for these syndromes is that their effects on the neuromuscular system are completely reversible. Hence, depletion of unbound toxin, pharmacologic modification of effects of bound toxin and appropriate management of respiratory and other complicating features of these syndromes should lead to complete recovery. Even though the toxins of the histotoxic clostridia produce irreversible damage, rational therapy which includes elimination of sources or conditions favoring production of toxins can lead to a favorable result.

In all of these syndromes, early recognition is a critical factor in determining outcome. In the case of botulism and tetanus, preventive measures have been highly efficient in the United States. In 1976 only 37 cases of botulism and 75 cases of tetanus were reported to the Center for Disease Control. The task for health care providers, then, is to maintain the effectiveness of these control measures and to remain alert to the possibility of encountering one or more of the sporadic cases which will occur inevitably.

The histotoxic clostridia pose a different problem. For example, C perfringens is a significant part of the normal bowel flora of a high proportion of humans. Prevention of infections by these organisms through immunization or other public health measures is not possible. Therefore, recognizing the settings in which they occur, minimizing factors favoring toxin production and responding appropriately when infection is recognized are the most effective control measures which can be applied at this time.

Recent recognition of infant botulism and elucidation of the mechanism by which C perfringens produces food poisoning suggest that the full story of the clostridial syndromes is not yet written. As research with these organisms and their toxins continues, we should anticipate delineation of new problems as yet unrecognized.

HARRY N. BEATY, MD
Professor and Chairman
Department of Medicine
The University of Vermont
College of Medicine, Burlington

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Hepatic Injury Due to Acetaminophen or Salicylates

EITHER SALICYLATES OR ACETAMINOPHEN, when taken in great excess, will regularly damage the liver. In particular, the ingestion of large amounts of acetaminophen leads to severe, often fatal, hepatic necrosis.[1] Elsewhere in this issue Babb summarizes recent reports that lesser amounts of these agents, when taken chronically, may cause hepatitis. This reflects toxic injury to the liver, not an allergic reaction to the drugs, and the effect is dose-related. Acetaminophen hepatotoxicity has been observed only when patients were taking at least three grams (about nine tablets) per day, usually more.

Similarly, most patients taking salicylates had serum salicylate levels above 20 mg per dl, though certain patients were quite sensitive to the drug. Unfortunately, salicylate levels of this magnitude are required for the antiinflammatory effect of salicylates. Worse, salicylate hepatotoxicity is potentiated in patients with active systemic lupus erythematosus (SLE)[2] and probably in patients with juvenile rheumatoid arthritis (JRA),[3] two diseases that are likely to require therapy with salicylates. If patients with active SLE or JRA are given antiinflammatory doses of salicylates, abnormal transaminase levels will develop in more than half.[2,3] If the salicylates have been of benefit, the physician may then have to consider exceptions to Babb's prudent advice that their administration should be stopped.

On the one hand, salicylate hepatitis is usually mild and reversible. Even if administration of salicylates is maintained, the hepatitis may improve—perhaps because as the disease improves it will no longer potentiate hepatotoxicity. In addition, as the salicylates lead to improvement their amount may be reduced, and this may be sufficient to allow resolution of the hepatitis. The salicylates have been in use for more than 100 years, with little evidence to suggest that they lead to chronic liver disease. There is less experience with the newer nonsteroidal antiinflammatory agents, such as ibuprofen and naproxen, which may also be hepatotoxic.[4-6]

On the other hand, in at least one patient chronic active hepatitis (reversible) has developed related to salicylate therapy.[7] Even more disturbing is a recent report of fatal hepatic necrosis in which aspirin was implicated as a possible contributing factor.[8]

Given these uncertainties, we have on occasion continued therapy in the face of abnormal serum transaminase levels of less than 200 U/per liter, but have ceased therapy in the face of rapidly rising levels or abnormal levels that persist beyond two or three months.

There are other clinical issues posed by salicylate hepatotoxicity. Should salicylates be used to treat arthralgias that may represent the prodrome of viral hepatitis? Should they be used in any patient with underlying liver disease? Are salicylates (or acetaminophen) responsible for a portion of the cases of chronic hepatitis? Are these agents more hepatotoxic than the newer nonsteroidal antiinflammatory agents? Will SLE or JRA potentiate the hepatotoxicity of drugs other than salicylates? Are there other diseases, or drugs, that potentiate the toxicity of these drugs?

The recently developed methods for studying the effects of acetaminophen or salicylates on cultured hepatocytes may help to better understand and to modify the effects of these agents on the liver.[9,10] In the meantime it appears that both drugs are reasonably safe in their common use as minor analgesics. When used in larger doses, the risk is greater and should be appreciated but, especially for the treatment of inflammatory arthritis, salicylates remain an important therapeutic agent. The comments by Babb will help us to use them with greater safety.

WILLIAM E. SEAMAN, MD
Assistant Professor of Medicine
University of California, San Francisco

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CASE REPORTS

Refer to: Fenster LF, Freeny PC, Beebe HG: Cavernous hemangioma of the liver presenting with fever—Successful treatment with prednisone. West J Med 129:138-140, Aug 1978

Cavernous Hemangioma of the Liver Presenting With Fever

Successful Treatment With Prednisone

L. FREDERICK FENSTER, MD
PATRICK C. FREENY, MD
HUGH G. BEEBE, MD
Seattle

A 43-YEAR-OLD WHITE WOMAN was admitted to another hospital on July 23, 1976, after a one-month history of malaise, myalgias, progressive weakness, shaking chills and fever to 39.5°C (103.0°F), with profuse night sweats. She had not responded to several different antibiotics given before admission. Physical examination showed no abnormalities except for hepatomegaly. The liver was felt 6 cm below the costal margin, with an overall span of 17 cm. Laboratory studies showed a sedimentation rate of 125 (normal to 20), hematocrit of 25 percent, leukocyte count of 8,900 cells per cu mm and normal findings on analysis of urine. Prothrombin time was 15.2 seconds (control 11.7). Serum bilirubin and glutamic-oxaloacetic transaminase values were normal. Serum alkaline phosphatase level was 104 IU (normal to 65). Four blood cultures, urine culture, and stool studies for ova and parasites were all negative. X-ray studies of the chest showed no abnormalities. Findings on an oral cholecystogram were normal. An upper gastrointestinal series showed displacement of the stomach posteriorly and laterally by an extremely enlarged liver. A barium enema study gave negative findings except for displacement by the liver. Gray scale ultrasonography showed an enlarged liver with multiple discrete areas of sonodensity. An intravenous pyelogram was negative. Liver scan with technetium colloid showed massive hepatomegaly with very little phagocytic activity in the entire right lobe and part of the left. An arteriogram was interpreted as showing hepatomegaly, vascular displacement and abnormal collections of contrast, consistent with neoplasm. A percutaneous liver biopsy study was attempted on August 2, 1976. Two passes were made, but only "gelatinous, bloody material" was obtained, without hepatic tissue being identified. The patient was transferred to Virginia Mason Medical Center on August 4, 1976.

In an effort to better define the limits of the process, with the possibility of surgical resection in mind, another arteriogram was carried out on August 6, 1976; it showed a cavernous hemangioma involving the entire right lobe of the liver. The left lobe appeared to be hypertrophied but otherwise uninvolved (Figure 1). Repeat studies showed a normal serum alkaline phosphatase value of 82 IU (normal to 90); serum glutamic-oxaloacetic transaminase value, 13 IU; hematocrit, 26.8 percent; cholesterol value, 104 mg per dl; prothrombin time, 14 seconds (control 12); platelet count, 300,000 per cu mm, and reticulocyte count, 5.1 percent. There were no burr cells noted on peripheral smear. Two additional blood cultures were negative. After observation for another week, during which the patient continued evening fever between 38.3°C and 38.9°C (101.0 and 102.0°F), the patient was taken to surgery on August 12, 1976, for right hepatic lobectomy.

From the Departments of Medicine (Dr. Fenster), Radiology (Dr. Freeny) and Surgery (Dr. Beebe), The Mason Clinic, Seattle.
Submitted April 20, 1978.
Reprint requests to: L. F. Fenster, MD, The Mason Clinic, 1100 Ninth Avenue, Seattle, WA 98101.

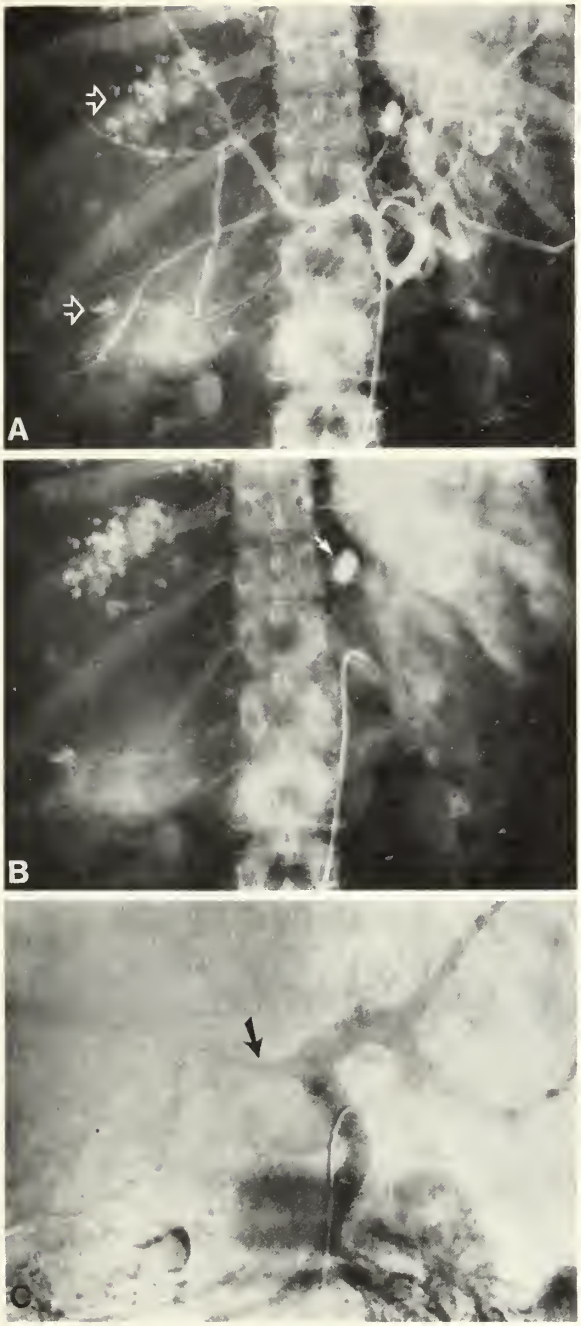

Figure 1.—Cavernous hemangioma. **A,** Celiac arteriogram, arterial phase. Liver is enlarged with displacement of normal size hepatic arteries and early filling of small, irregular vascular spaces (open arrows). The left lobe is enlarged but otherwise normal. **B,** Celiac arteriogram, late venous phase. There is persistent filling of the vascular spaces in the right lobe. The most medial collection **(arrow)** was felt to be in the superior-medial segment of the right lobe. No contrast collections seen in left lobe. **C,** Portal venous phase of priscoline-augmented superior mesenteric arteriogram (subtraction). The main branch of the right portal vein is occluded **(arrow).** The left portal veins show displacement, consistent with hypertrophy, but no occlusions.

At surgical operation, the liver was found to be enlarged, with a sponge-like consistency that would compress and then promptly refill—typical of diffuse hemangioma. High on the posterior dome of the right lobe there was a more firm, well-demarcated area consistent with thrombosis of a portion of the hemangioma. After due consideration of the risks of precipitating hemorrhage, multiple needle aspirations were carried out to find any abscesses, but none was found. Several liver aspiration cultures were done which were sterile. It was the opinion of the surgeon, and a pathologist present in the operating room, that both lobes were diffusely involved by cavernous hemangioma and no resection was possible. A biopsy study was deemed too risky. The remainder of the abdominal exploration gave negative findings.

The postoperative convalescence of the patient was uncomplicated except for continued fevers to 38.3°C (101.0°F) each day, despite around-the-clock acetaminophen. She was discharged home and her fever increased to 39.5°C (103.0° F) again, with drenching sweats and continued weakness. On August 27, 1976, the patient was started on a regimen of prednisone, 10 mg twice a day, and the fever promptly disappeared and she began to feel better, except for continued fatigue. Prednisone administration was gradually tapered. When receiving 10 mg per day, the patient had a low-grade fever in the evening, never over 37.8°C (100.0°F). By October 20, 1976, she was feeling much improved and the liver seemed slightly smaller on physical examination, being felt 4 to 5 cm below the costal margin. By January 5, 1977, the patient had gained weight, was feeling better, and was afebrile on a regimen of 5 mg of prednisone per day. Her hematocrit value was now normal at 38 percent. Administration of prednisone was tapered off by February 1, 1977, and there has been no recurrence of fever a year later. On January 16, 1978, a repeat ultrasound examination was done and showed the right lobe of the liver to be slightly smaller than on her preoperative study.

Discussion

This case is being reported because of two unusual aspects which deserve attention. First, the predominant clinical presentation of this patient's giant hemangiomatous liver was high fever, shaking chills and drenching night sweats, documented over nine weeks. Second, the fever

responded dramatically to moderate doses of prednisone, with gradual improvement in other clinical measures—such as hematocrit, weight, and ability to work; these improvements have been sustained long after cessation of steroid therapy.

Cavernous hemangiomas of the liver in adults usually present with some combination of abdominal mass, pain, or symptoms resulting from compression of other adjacent organs. Rarely, spontaneous hemorrhage results in an acute hemoperitoneum, with high mortality. Fever has only rarely been mentioned in the literature as a manifestation of this entity. Shumacker, in a review of 67 cases, noted one patient whose chief complaint was evening fever, and one other patient with low-grade fever.[1] Levitt and co-workers reported about one patient with fever to 103°F.[2] Adam and associates reviewed 22 cases of massive hemangioma of the liver; fever was not mentioned.[3] Kato and co-workers reviewed 55 cases from Japan and mentioned three patients with fever, but no details were given.[4] Okazaki and associates recently reported experiences with radiation therapy of cavernous hemangiomas and noted one patient presenting with persistent spiking fever that gradually resolved after radiation therapy.[5]

Corticosteroid therapy is the treatment of choice in children with massive cavernous hemangiomas of the skin and subcutaneous tissues, although the mechanism of its efficacy is unknown.[6] Treatment of liver hemangiomas with steroids has rarely been reported. Goldberg and Fonkalsrud reported the successful use of steroids in a young infant with life-threatening high output congestive heart failure due to a liver hemangioma, with dramatic shrinkage of the liver resulting.[7] Slovis and associates used steroid therapy, along with digitalis and radiation therapy, in the management of four infants with this disease, all presenting as high output heart failure. Although these patients eventually did well, the efficacy of steroids was difficult to assess.[8] We have been unable to find any published experiences with steroid therapy of hemangiomas of the liver in adults.

Our patient refused radiation therapy, and her temperature elevations did not respond to acetaminophen administration. The rapid suppression of fever—along with progressive improvement in general well-being, anemia, weight and ability to work—suggests that the prednisone therapy was efficacious above and beyond merely acting as a nonspecific antipyretic. A follow-up arteriogram has not been done, and a repeat ultrasound examination showed only minimal decrease in liver size. The mechanism of both the fever and the possible beneficial effect of prednisone is speculative. It is tempting to suppose that injury to blood cells, especially polymorphonuclear leukocytes, in the eddies and currents of the hemangioma leads to release of pyrogens and hence a centrally mediated fever. It is known that hematomas per se may be the cause of fever, and certainly clotting occurs commonly in hemangiomas, sometimes resulting in calcifications in the lumens.[9,10] Corticosteroids have long been known to have antipyretic as well as anti-inflammatory actions. The mechanism of this fever suppression is not known, but there is experimental support for both central effects on the temperature regulation center in the hypothalamus,[11] and peripheral effects on pyrogen release by leukocytes.[12]

Summary

A patient with cavernous hemangioma of the liver presented as a fever of unknown origin. After surgical resection was found to be impossible, and radiation therapy refused, corticosteroid therapy was instituted empirically, with prompt resolution of the fever and apparent improvement in other manifestations of the disorder. The pathogenesis of the fever and the mechanism of the response to steroid therapy are speculative.

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Refer to: Halpern AA, Jameson RM, Nagel DA, et al: Nontraumatic embolic clostridial gas gangrene—Involvement of an extremity associated with endoscopy. West J Med 129:141-144, Aug 1978

Nontraumatic Embolic Clostridial Gas Gangrene

Involvement of an Extremity Associated With Endoscopy

ALAN A. HALPERN, MD
ROBERT M. JAMESON, MD
DONALD A. NAGEL, MD
DAVID J. SCHURMAN, MD
Stanford, California

THE NON-TRAUMATIC DEVELOPMENT of clostridial gas gangrene in an extremity is an unusual and generally lethal occurrence; consequently, rapid diagnosis is essential. Only 22 cases have been described previously. In such cases the clostridial organisms presumably are transported to a peripheral site from the gastrointestinal tract, either directly or through metastatic transmission.

Report of a Case

A 27-year-old woman was seen in consultation by the orthopedic service at Stanford University Medical Center when she was found to have a pulseless, cold, cyanotic, right upper extremity.

In 1971 a diagnosis of nodular sclerosing Hodgkin disease, stage III-A, had been made. The patient was given multiple treatments of irradiation and did quite well until July 1976, when fever and explosive, watery diarrhea developed. When admitted to the medical center her temperature was 38.8°C (101.8°F), pulse 112, and blood pressure 104/70. The lungs were clear, and the heart had a regular sinus rhythm with a grade II/VI systolic ejection murmur. Examination of the abdomen showed no abnormalities. Examination of the extremities showed no edema, cyanosis, clubbing or tenderness, and all pulses were present bilaterally. The leukocyte count was 12,500; hematocrit reading, 36.9 percent, and platelet count, 230,000. The level of alkaline phosphate was 876, bilirubin, 4.4; albumin, 3.3; lactate dehydrogenase, 471; serum glutamic oxaloacetic transaminase, 277; leucine aminopeptidase, 189, and nucleotidase, 172. The sedimentation rate was 53. A liver scan, rose bengal study, and abdominal ultrasound examination all gave findings within normal limits. Cultures of urine, sputum, stool and blood specimens were negative. During the patient's hospital stay, fevers spiked daily to 39°C. A liver biopsy study showed extensive inflammatory reaction surrounding the portal triads. Twenty-four hours later bloody stools developed. A barium enema study showed thickened folds in the cecum and ascending colon. A bone marrow aspirate showed decreased megakaryocytes with moderate hypoplasia. The diarrhea persisted, associated with a decreasing hematocrit reading and a platelet count of 8,000.

Transfusion was carried out with packed cells and platelets. An upper gastrointestinal series showed impaired distensibility of the distal stomach and antrum. On the day before development of a cyanotic pulseless extremity (13 days after admission), endoscopy was carried out. The

Figure 1.—Roentgenogram of the right arm shows the gas in the tissues.

From the Division of Orthopedic Surgery, Stanford University Medical Center, Stanford.

Submitted, revised, October 19, 1977.

Reprint requests to: Alan A. Halpern, MD, Division of Orthopedic Surgery, Stanford University Medical Center, Stanford, CA 94305.

stomach and duodenum appeared erythematous with patchy hemorrhages and ulceration. The duodenal biopsy specimens showed Gram-positive rods; there was no gas in the tissue, however. During the day, dyspnea and pitting edema of the lower extremity developed. An x-ray study of the chest showed a pleural effusion and interstitial edema. A left thoracentesis yielded 700 ml of fluid. The patient remained febrile at 38°C (100.4°F), and her pulse rate gradually increased.

An intravenous line was placed in the patient's right arm. Approximately 12 hours later the patient complained of some moderate pain. Four hours later, the arm became more painful and was swollen and erythematous. A discrete nummular lesion with a dusky appearance was seen on the volar surface, just opposite the intravenous site. However, it was specifically noted that this area was not adjacent to the site of the intravenous line. Three hours later, the arm was swollen to the level of the elbow and the intravenous line was removed, but the patient's arm became progressively more painful and at 7:00 a.m. was noted to be crepitant, mottled, discolored, pulseless, and lacking sensation or motor function (Figure 1). Aspiration from a vesicle revealed Gram-positive rods.

At surgical operation, purpuric lesions extending the full length of the right arm, including the right breast and right lateral chest margin, were present (Figure 2). There was extensive necrosis of the entire deltoid, biceps and forearm muscles. A musty smelling gas exuded from all muscular compartments that had been released by the fasciotomy. A forequarter amputation was carried out. Povidone iodine soaked sponges were placed in the wound and the edges were loosely approximated with a bulky dressing. A dopamine drip was required to maintain blood pressure, and a volume respirator to maintain respiratory function. On the second postoperative day, respiratory function could not be maintained and the patient died.

At autopsy lymphomatous, nodular involvement of the small and large bowel were noted,

Figure 2.—Vesicular lesions cover the axilla and entire arm.

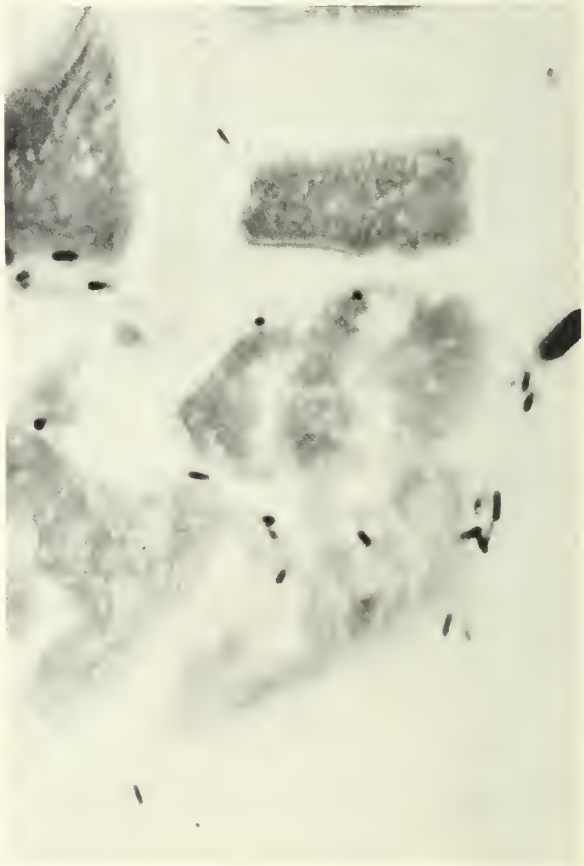

Figure 3.—Microscopic examination of the muscle shows Gram-positive rods.

with multiple ulcerations. The cecum was particularly involved with the nodular lesions. Microscopic examination of the amputated extremity showed widespread myonecrosis. Prominent interstitial edema with large Gram-positive rods appeared in the muscle (Figure 3); these were identified as Clostridium perfringens.

Comment

Gas gangrene is a rare infection caused primarily by organisms of the genus Clostridium, an anaerobic microaerophilic Gram-positive rod which produces endospores.[1,2] Approximately 30 percent of war wounds harbor Clostridium; however, actual clostridial gas gangrene infection develops in less than 5 percent of these wounds. As Ogilvie has noted, the development of gas gangrene is associated with a particular opportunity, rather than a particular organism.[3]

While most cases of gas gangrene have been found in dirty, necrotic, open wounds, and in cases of criminal abortions and contaminated abdominal operations, a growing number of cases have been documented in which no open trauma occurred (Table 1).[4-19] In addition, more than 200 cases of gas gangrene complicating intramuscular injections, particularly of adrenalin, have been documented.[1,20]

Clostridial sepsis has been described unassociated with any open trauma.[4,21-31] In most of these a malignant condition has been found with epithelial ulcerations of the gastrointestinal tract frequently present.

Under normal circumstances, the gastrointestinal tract, particularly the colon, is a repository for clostridial organisms. However, infection does not result unless suitable anaerobic conditions develop. In the compromised host, as the result of neoplastic or hematologic disease, the gastrointestinal tract may serve as the portal of entry for infection with Clostridium organisms.[1] This may result in sepsis or focal involvement of an extremity. Minimal trauma may furnish the decreased oxidation-reduction potential necessary for the multiplication of the organism.

Because gas gangrene is usually unsuspected unless associated with open trauma, the failure to diagnose this condition promptly has probably contributed to the poor prognosis in almost all cases. In one case the subcutaneous emphysema of the thigh was noted only at autopsy.[15]

The patient presented in this report had Hodgkin disease and gas gangrene of the right arm developed. While the gas gangrene developed following endoscopy, and duodenal biopsy, this could certainly not be implicated with any cer-

TABLE 1.—*Case Reports of Nontraumatic Gas Gangrene*

Author	*Year*	*Primary Diagnosis*	*Extremity*	*Organism*	*Complications*	*Course*
Gordon[7]	1936	Appendiceal abscess	Thigh	Perfringens	.....	Died
Wyman[19]	1949	Carcinoma of colon	Thigh	.....	.....	Died
Kimball and Rawson[11]	1952	Carcinoma of colon	Thigh	.....	.....	Died
		Carcinoma of colon	Arm	.....	.....	....
Valentine[18]	1957	Adenocarcinoma cecum	Hip	Septicum	.....	Died
Smucker et al[16]	1960	Adenocarcinoma cecum	Thigh and buttocks	Perfringens	Appendicitis	Died
Soscia and Grace[17]	1965	Necrotizing pancreatitis	Leg	Perfringens	Acute cholecystitis	Died
Isenberg[9]	1966	Diabetes	Thigh	Perfringens	.....	Died
Rose and Bukosky[15]	1966	Duodenal ulcer	Thigh	Perfringens	.....	....
Gazzaniga[6]	1967	Adenocarcinoma cecum	Arm	Perfringens	Diabetes	Died
Marty and Filler[12]	1969	Adenocarcinoma colon	Forearm	Perfringens	Diabetes	Died
		Duodenal ulcer	Leg	Perfringens	Diabetic ketoacidosis	Died
Alpern and Dowell[4]	1969	Cyclic neutropenia	Thigh	Septicum	.....	Lived
El Dahla[5]	1971	Ischiorectal abscess	Leg	Perfringens	.....	Died
Kapusta et al[10]	1972	Neutropenia	Thigh	Perfringens and septicum	.....	Lived
Poretz et al[14]	1974	Adenocarcinoma colon	Thigh	Septicum	.....	Died
Mzabi et al[13]	1975	Adenocarcinoma cecum	Leg and foot	Septicum	Diabetes, atherosclerosis	Died
		Adenocarcinoma cecum	Thigh	Tertium	Diabetes	Died
Hedstrom[8]	1975	Perforated intestine	Thigh	.....	.....	....
		Perforated intestine	Thigh	.....	.....	....
		Acute leukemia	Thigh	.....	.....	....

tainty. A compromised mucosa was shown, however. The infection of the right upper extremity was unassociated with any known trauma or direct extension from the gastrointestinal tract. As in almost all other cases, the disease followed a rapid, fatal course.

Summary

A case of nontraumatic gas gangrene of the right arm is presented in a patient with Hodgkin disease. Endoscopy had been carried out on the previous day, with Gram-positive rods shown in the duodenal biopsy specimen. In all, 22 cases of nontraumatic gas gangrene of the extremities have been described, with a malignancy of the gastrointestinal tract present in most of them.

This case is presented to alert surgeons to the possibility of nontraumatic clostridial gas gangrene in any patient in whom an unexplained painful extremity suddenly develops, particularly in a patient with a gastrointestinal neoplasm or ulceration. Early diagnosis and treatment may improve the prognosis, even in the compromised host.

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Refer to: Sawada S, Fye KH: Tennis elbow as a complication of pollicization of the index finger. West J Med 129: 144-146, Aug 1978

Tennis Elbow as a Complication of Pollicization of the Index Finger

SHIGEMASA SAWADA, MD
KENNETH H. FYE, MD
San Francisco

THE LAST 30 YEARS have seen dramatic advances in surgical procedures of the hand. Surgeons have developed techniques for the reattachment of amputated digits[1-3] and the autotransplantation of intact digits.[4,5] New thumbs can now be created by autotransplantation of the hallux[5] or pollicization of the index finger.[6]

We recently saw a patient who had undergone a pollicization procedure of his left index finger following a traumatic amputation of his left thumb. Although the local results of the operation were excellent, severe, recurrent left lateral epicondylitis had developed. The development of epicondylitis in a patient whose thumb and fingers are extended by the same extensor muscles has not, to our knowledge, been previously reported.

Dr. Sawada is Arthritis Foundation Fellow, Veterans Administration Hospital, San Francisco, and Dr. Fye is Assistant Professor of Medicine, University of California, San Francisco, and Veterans Administration Hospital, San Francisco.

Submitted, revised, October 26, 1977.

Reprint requests to: Kenneth H. Fye, MD, Immunology and Arthritis Section (151T), Veterans Administration Hospital, 4150 Clement Street, San Francisco, CA 94121.

Report of a Case

A 56-year-old carpenter was in good health until June 1971 when his left thumb was severed while he was working with a table saw. Since the amputation occurred through the distal first metacarpal, the carpometacarpal joint remained intact. In February 1972 a pollicization procedure of the left index finger was done at Stanford University Hospital. The proper bone length of the new "thumb" was determined by x-ray examination of the right hand. The excess metacarpal shaft from the index finger was used as an intramedullary bone graft between the transposed finger and the remainder of the first metacarpal. The volar interosseous muscle of the index finger was dissected free from its insertion and allowed to contract. It was used to provide bulk for the new web space which was created out of skin flaps.

By June 1972 the new "thumb" could be bent passively, but the patient could not oppose the tips of his thumb and middle finger. By July 1972 the thumb could be actively flexed and used to oppose the middle finger. The pollex function of the new thumb was almost normal by September 1972.

The patient did well until November 1976, when he presented to the Veterans Administration Hospital in San Francisco, with a three-month history of left lateral epicondylar pain, worsened by pronation of the wrist. There was no swelling or erythema. There were no other joint symptoms.

Findings on physical examination in November 1976 were normal except for the left arm. There was exquisite tenderness over the left lateral epicondyle. The discomfort was notably increased by pronation of the wrist or extension of the fingers against resistance. The left elbow had full range of motion, and there were no signs of articular inflammation. Examination of the left hand showed three fingers and a "thumb" with proximal and distal interphalangeal joints (Figure 1). The "thenar eminence" was atrophic, but grip strength was good.

The laboratory data included normal findings on a complete blood count, an erythrocyte sedimentation rate of 8mm per hour (Wintrobe) and findings within normal limits on analysis of urine. A Venereal Disease Research Laboratories study was negative, and the patient had no serum rheumatoid factors or antinuclear antibodies. The uric acid was normal. Findings on an electrocardiogram and x-ray study of the chest were within normal limits. Radiographs of the left elbow showed no abnormalities. Radiographic examination of the left hand showed an amputation of the index finger through the metacarpal with transplantation of the digit onto the first metacarpal. The "thumb" had two interphalangeal joints (Figure 2).

Figure 1.—Photograph of left hand showing long-term results of pollicization of left index finger.

The patient was felt to have a left lateral epicondylitis. His condition responded dramatically to the injection of 20 mg of triamcinolone acetonide (Kenalog®) and 0.5 ml of 1 percent xylocaine directly into the point of tenderness over the lateral epicondyle and to the institution of therapy with orally given tolmetin. He was asymptomatic until March 1977, when he had to use a screwdriver with his left hand. Within 24 hours the left lateral epicondylitis recurred. He returned to the San Francisco Veterans Administration Hospital for another steroid injection, again with dramatic relief.

Discussion

Both the cause and pathogenesis of epicondylitis, or tennis elbow, remain obscure. It has been hypothesized that epicondylitis is, in fact, a radiohumeral bursitis or synovitis.[7] Some investigators have hypothesized that the inflammation is due

Figure 2.—Radiograph of the left hand showing surgical amputation of the index finger through the second metacarpal, with grafting of the digit onto the first metacarpal.

to the deposition of calcium salts in the adventitia surrounding the origin of the forearm extensors.[8] Others have described minute tears in the tendons themselves.[9] Much of the discomfort associated with the disorder is thought to be due to entrapment of the radial nerve and its branches, particularly the posterior interosseous nerve.[10,11] Fibrillation of the articular cartilage of the head of the radius[12] and periosteal damage with accompanying periostitis or myositis, or both,[13] have also been suggested as etiologic mechanisms.

Even though there is controversy over the precise pathogenesis, the condition is almost universally considered to be associated with chronic degenerative and inflammatory changes in tissues surrounding the origin of the long extensors of the fingers. It usually occurs in people who use their hands a good deal,[14] including some tennis players.[15,16] In these patients other soft tissue inflammatory lesions often develop, such as rotator cuff inflammation, bicipital tendinitis, de Quervain tenosynovitis and trochanteric bursitis.[14]

Our patient was right-handed, but the epicondylitis developed over the left lateral epicondyle. We hypothesized that since the erstwhile left index finger was now a "thumb," the long extensors and flexors of the fingers must have been subjected to increased stress. The same extensors had to continually oppose themselves in the constant pinch and grip activity of everyday life.

The patient's condition has so far responded to conservative therapy, and we have no plans to carry out a corrective surgical operation over the lateral epicondyle.

This case reemphasizes the possible relationship of epicondylitis with stress on the long extensors of the fingers. We wonder whether other patients who had had pollicization procedures of the digits have developed similar problems.

Summary

In a 56-year-old man, severe, recurrent left lateral epicondylitis (tennis elbow) developed four years after pollicization of the left index finger was done. The condition may have developed because of increased stress on the long extensors, which must extend both the "thumb" and the fingers.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Lithium Therapy in the Elderly

To the Editor: This is in response to the article "Lithium Treatment for Psychiatric Disorders" (West J Med 128:488-498, June 1978). The authors state that lithium is a safe drug for the elderly. Although they correctly state that the dose should be reduced, they fail to elaborate on this point.

Although lithium appears to be as effective in the control of manic states in the elderly as it is in younger patients with cyclic mood disorders, clinical experience in the elderly has shown that severe reactions to the drug could develop quite rapidly, sometimes as early as 15 minutes after an initial dose. All of the usual toxic side effects of lithium are seen in the elderly, as well as in the young. However, particular attention has been focused on the frequent appearance of an acute brain syndrome (associated with neuromuscular irritability and impaired consciousness) as a predominant sign of lithium toxicity.[1] Crews and co-workers[2] suggested that lithium toxicity may be expressed as an aggravation of a tardive dyskinesia already present to a minimal degree, while others suggest that lithium might improve this syndrome.[3] Friedman[4] states that elderly patients are more susceptible to the cognitive effects of lithium, although no one knows the natural history of manic depressive illness, with or without therapy. Others have also commented that patients will complain of subtle memory loss while taking lithium, and report a return to normal memory after discontinuing the drug.

In order to avoid such problems, a dose titration has been devised and used over the years. There seems to be agreement that dosage of lithium should be initiated at well under 900 mg per day.[5,6] The need for lower daily doses to achieve adequate blood levels relates to the longer half-life of lithium in the elderly. The half-life in the aged is twice that of younger patients, and because lithium is primarily excreted in the urine, the prolonged half-life is related to renal aging. It seems that serious side effects in the elderly occur on lower doses and at lower blood levels, but that there are no reports of serious side effects when lithium dosage is under 900 mg daily or when serum levels are under 1.0 mEq per liter. This lack of toxicity is consistent with initiating treatment at doses well under 900 mg per day, while at the same time maintaining a therapeutic response.

So in summary it can be said that lithium has been found to be quite effective in treating cyclic mood disorders in the elderly, and if the practitioner is aware of the problems of lithium use in the elderly, toxic side effects can be avoided.

REIN TIDEIKSAAR, RPA-C
Jewish Institute For Geriatric Care
Long Island Jewish-Hillside Medical Center
New Hyde Park, NY
Clinical Instructor
Health Sciences Center
State University of New York at Stony Brook
Stony Brook, NY

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Lithium Treatment—A Correction

To the Editor: In the article on lithium therapy in the June issue (Maletzky BM, Shore JH: Lithium treatment for psychiatric disorders. West J Med 128:488-498, June 1978) there appears to be a serious error in Table 2 on page 494 concerning guidelines for the use of lithium in women of childbearing potential or who are pregnant.

The general theoretical consideration is that lithium is in equilibrium across the placental membrane and the amount of lithium in the

serum of the mother is equivalent to that amount of lithium to which the fetus is exposed.

Under F2 in this table, there is the following statement: "Use three times daily dose, or if available, sustained-release tablets. Avoid large single or double daily doses."

Using three times the daily dose could be severely toxic to the mother and fetus and could result in serious complications and even death.

In an attempt to avoid large single or double daily doses one would not use three times the daily dose. Instead, the usual procedure if lithium must be used during pregnancy is to divide the usual daily dose into more frequent administration of the lithium thereby avoiding more concentrated pulses of lithium that might adversely affect the fetus. *Do not use three times the daily dose* as this could be severely toxic to the mother and the fetus. Instead, use the lowest effective dose and divide the dosage into more frequent administrations.

A list of other articles published on this subject appears below.

MICHAEL D. GOLDFIELD, MD
Department of Psychiatry
University of California, San Francisco

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The Authors Reply

To the Editor: We thank Dr. Goldfield for his correction. In proofing the typescript of our article we missed this error. F2 in Table 2 should read "Use in divided doses, preferably three times a day, or, if available, sustained-release tablets. Avoid large single or double daily doses."

JAMES H. SHORE, MD
BARRY M. MALETZKY, MD
Portland, Oregon

Hysteria by Any Other Name

To the Editor: On page 482 of the June issue there appeared an article by Dr. James R. Morrison entitled "Management of Briquet Syndrome (Hysteria)."

I have one objection: hysteria is not a syndrome but a well-known clinical entity. To attach the name Briquet to it because Briquet published a book on hysteria in 1859 is not justified. Moses Maimonides (1135 to 1204) described conversion hysteria as occurring long before the birth of Christ.

JULIUS BAUER, MD
Beverly Hills, California

* * *

The Author Replies

To the Editor: Conversion hysteria is certainly an ancient affliction, but so is "hysteria" an ancient term—so old that it has been applied to a number of conditions. That is the point of the new term: to distinguish the collection of symptoms we now call Briquet syndrome from other, less well-defined usages.

Careful definition of this condition makes possible effective management. That was a major point of my article. Thank you for enabling me to make it again.

JAMES R. MORRISON, MD
Oceanside, California

Trauma Rounds

Chief Discussant
JAMES M. WILSON, MD

Editors
DONALD D. TRUNKEY, MD
F. WILLIAM BLAISDELL, MD

This is one of a series of Conferences on Trauma at San Francisco General Hospital

Refer to: Wilson JM: Shotgun ballistics and shotgun injuries (Trauma Rounds—San Francisco General Hospital). West J Med 129:149-155, Aug 1978

Shotgun Ballistics and Shotgun Injuries

IAN LEVERTON, MD:* The patient is a 25-year-old white man who was admitted to the emergency department 20 minutes after having been shot in the right lateral thorax and right thigh with a 12-gauge shotgun. The estimated range was 5 to 10 yards; the empty shell casings at the scene confirmed the gauge and the fact that 00 buckshot had been the load. Upon physical examination, the patient was conscious and had a blood pressure of 70 systolic, a pulse of 120 and respiration of 34. There were multiple pellet holes in the right lateral thorax and right upper quadrant with injuries of the left forearm and left hand as well. There were multiple pellet holes in the right lateral thigh with an obvious fracture of the right femur. There were no pulses distal to the blast area in the thigh, and the foot was cold and ischemic.

Cutdowns were carried out in the left arm and left leg, and Ringer lactate was infused rapidly. Blood was drawn and sent for typing and cross matching, and x-ray films of the femur, abdomen and chest were taken en route to the operating room. At operation, four tangential wounds of the liver and omentum were seen. The tenth rib was shattered, producing a large tangential diaphragmatic defect. The diaphragm was repaired, the liver lacerations which were not bleeding were drained posteriorly, and bleeding points in the omentum were controlled. Local debridement of the entrance wounds was also carried out. Simultaneous exploration of the thigh showed a totally transected superficial femoral artery. The damaged segment was resected and primary anastomosis was carried out. Soft tissue debridement was done and an angiogram taken. Arteriography showed patent anastomosis but narrowing of the vessels in the thigh. The patient was placed in skeletal traction and transferred to the intensive care unit.

The patient's course was relatively benign and he was transferred from the intensive care unit on the sixth postinjury day. At present he is being managed in traction for his femur injury.

F. WILLIAM BLAISDELL, MD:† I would like to introduce our chief trauma resident, Dr. James Wilson, who during several years in the navy did special research on ballistics and wounding characteristics of missiles. Dr. Wilson, would you

Sponsored by the American College of Surgeons Northern California Trauma Committee. Supported in part by NIH Grant GM118470.

*Junior resident in surgery, San Francisco General Hospital.

Reprint requests should be sent to: Donald D. Trunkey, MD, Department of Surgery (3A), San Francisco General Hospital, 1001 Potrero Avenue, San Francisco, CA 94110.

†Former Chief, Surgical Service, San Francisco General Hospital. He is now Professor and Chairman, Department of Surgery, University of California, Davis, School of Medicine.

comment on the nature of shotgun injuries and principles of their management?

JAMES M. WILSON, MD:* If one were to analyze the factors most strongly influencing patient fatality following gunshot wounds in the civilian population, it would become immediately apparent that the type of weapon used is key, and that shotguns are responsible for a greater percentage of deaths than are any other type of firearm. Shotgun wounds are different from rifle and pistol wounds and by no means can be considered identical either from a ballistics standpoint or in wounding capability.

Shotguns are popular worldwide; more of these smooth-bore weapons are bought and used than are rifled types. In fact, many governments—such as those of Great Britain and the Soviet Union—discourage the use of rifles yet allow unrestricted use of shotguns.

The idea of using a blast of small pellets for hunting and even for fighting is as old as the use of firearms itself. The first guns were smooth bore or unrifled and as a result were grossly inaccurate. Rifling, or the grooving of the gunbarrel to produce spinning of the projectile, was not developed until about 1500—some 150 years after gunpowder was first used as propellant. Early American colonists began to use buckshot loads in their flintlock muskets because the general accuracy of the smooth bore barrel weapons was so poor. Use of buckshot also made it easier to hit moving targets or those in brush, where quick shooting was essential for acquiring food or for protection.

Modern shotguns date back to about 1750 when flintlock, and later percussion, caps were used. The LeFaucheaux pinfire was patented in 1836; this type of shell is still made and used in certain parts of Europe. In 1851 Charles Lancaster of England developed an improved centerfire breech-loading shotgun—a development which marked the end of the muzzle-loader era. Choke boring, or the narrowing of the end of the barrel to improve target coverage by pellets, was little known or used until about 1870. In that year, Fred Kimble of the United States developed it to near its present form.

In relation to powder charge, the first commercially successful smokeless powder was developed in 1864 by a Prussian, Captain E. Shultz. Earlier smokeless powder burned too fast, generating excessive pressures whereas Shultz's powder which burned slower was made from nitrated wood pulp, using a method which duPont later used for many years in the United States.

TABLE 1.—*Common Shotgun Gauges and Corresponding Calibers*

10 gauge	0.775 caliber
12 gauge	0.730 caliber
16 gauge	0.670 caliber
20 gauge	0.615 caliber
28 gauge	0.550 caliber
410	0.410 caliber

Modern shot of uniform quality was developed by the Englishman William Watts in 1769. He dropped specific amounts of hot lead into a column of water, thus producing lead pellets.

As mentioned earlier, modern shotguns are smooth bore—that is, the barrels are smooth without any rifling or grooving. Shotguns come in almost every form imaginable: single shot, double-barreled side-by-side, double-barreled over-and-under, pump action or semiautomatic. The Winchester Model 97 pump action shotguns were used by American troops in short barrel form during World War I. A similar gun was used in World War II and in Vietnam for jungle fighting. Police have used this same riot gun—a 12 gauge with a sawed-off (20-inch) barrel loaded with double 0 buckshot. The advantages of this gun as a close range weapon will be made clear later in this text.

The gauge (or bore caliber) for a shotgun is designated differently than for a rifle or pistol. The classification system is antiquated, dating back to muzzle loading days. At that time, the gauge of a musket was expressed in terms of how many lead balls of an appropriate size would be required to weigh one pound. Therefore, a 12-gauge weapon originally had a bore of such diameter that a round lead ball weighing 1/12 pound could enter the barrel. This system of designation has persisted to modern times although there are two exceptions to the system: the 9-mm shotshell which has, indeed, a 9-mm bore, and the 0.410 gauge which is actually 0.410 caliber; that is, 0.410 inches in diameter. The common shotgun gauges are shown in Table 1 with their corresponding calibers.

The larger gauge guns—4, 8 and 10 gauge—have essentially disappeared from popular use since the advent of higher grade smokeless powder and of choke boring, which notably improved the performance of the smaller gauge weapons.

*Senior Resident, Surgical Service, San Francisco General Hospital.

The 12 gauge is by far the most popular shotgun ever used in the United States for civilian sports and for military, police and criminal use. Indeed, more than half of the shotguns sold in this country each year are 12-gauge weapons. The 12, 16, 20 and 410 gauge are extensively manufactured and used in the United States but the advantages of each are a function only of personal preference, as we will show in the discussion on ballistic characteristics which follows.

The choke of a given shotgun designates the amount of constriction at the end of the weapon barrel, and it is the choke that actually determines the shot pattern at a given distance from the muzzle. The constriction acts much like the nozzle on a garden hose which, when partially constricted, gives a narrow stream of water for maximum shooting distance for a given, constant pressure. Full choke (or tight constriction), modified choke and cylinder bore (or no constriction) constitute the three basic types of barrels. A full-choke barrel will force approximately 70 percent of the pellets in a charge into a pattern circle with a 30-inch diameter at a 40-yard range; modified choke gives 60 percent and cylinder choke propels only 40 percent of the pellets into this circle pattern area. The velocity of the individual pellets is affected very little by choke or barrel length. Consequently, the choke of the barrel will directly affect the pattern or concentration of the pellets. Obviously, range will be the main determinant of the actual target pattern using any given choke. Sawed-off shotguns or riot guns, such as those used by police and in Vietnam produce an even wider pattern than do cylinder bore weapons; the reason for this is that they are not designed for range but more for target coverage at close range.

The ammunition unit is called a shot shell and consists of a plastic casing (or paper casing, in older shells) compressed into a brass cup which contains the primer. The powder is then compressed into the primer cup at the base of the shell. Next, a wad of plastic or paper, is placed between the powder and the shot charge and the shot is held within the casing by another thin wad of paper or plastic. The whole system is then compressed and the top edge of the casing crimped. When the gun is fired, it is the shot charge, along with the wadding, that leaves the barrel. Therefore, at close range a victim is hit not only by pellets but also by the wadding and casing debris.

One additional point about the powder deserves comment. As aforementioned, shotgun powder is quite fast burning and is designed for use only in shotguns where relatively low chamber pressures are generated. As a result, serious injury will be inflicted if this powder is used by novices in home-loading rifle or pistol cartridges.

The shot, then, is a collection of individual pellets. They were once made of pure lead but are now usually made of a lead and antimony alloy. Problems with pellet deformity and fouling of the barrel subsequently led to the practice of coating the pellets with a copper-zinc alloy. This coating is especially common in magnum loads.

The pellets come in various sizes and are loaded into the shot shells usually in increments of approximately one ounce. The No. 6 shot is the most common shot load used; it is designed for use on most medium-sized fowl and, when used in 12-gauge weapons, is an excellent all-around shell. Therefore, because the No. 6 shot shell used in a 12-gauge weapon is the most popular combination, it is the one most commonly involved in shotgun wounds. The No. 6 pellet is 0.11 inches in diameter and each shell contains 340 pellets (weighing about 1½ ounces). At close range, therefore, the concentration of pellets within the target pattern is extensive.

The other type of pellet which is worthy of special mention is the No. 00 buck; this was the size pellet used to wound the patient presented today. The double 0 buckshot was designed originally for killing larger animals and its diameter is 1/3 inch.

The shot charge radiates from the muzzle in a cone-like distribution and the pellets should be evenly distributed at the base of this cone. The pellet distribution is known as the "shot pattern" and is dependent, as mentioned earlier, upon the choke of the barrel and the range at which the shell is fired. Effective range for most shotguns is 20 to 40 yards from the target. At a range of under 20 yards, the dense shot pattern destroys most game being shot. while at more than 40 yards the pattern is too sparse to give any effective killing power. The shotgun is seldom used against humans at a range of over 40 yards, as most shotgun wounds seem to be inflicted at close range—15 yards or less.

From a ballistics standpoint, the shotgun is quite different from the single projectile, high-velocity rifle. In the case of the latter, all ideal characteristics of a projectile—good ballistic

shape, high sectional density, high velocity and deep penetration with controlled expansion—are met. But in the shotgun, all these ideal properties are sacrificed in order to obtain target area saturation, therefore making it possible to hit a small, fast-moving target.

The wounding capacity of a given weapon is a function of both the projectile mass and its velocity. Consequently, shotgun wounds should be classified along a wide spectrum ranging from injury inflicted by a single pellet to that caused by an entire charge of hundreds of pellets together with wadding and debris, which all enter the victim.

As stated earlier, range is the major determinant of wounding capacity using any given load. When a 12-gauge shotgun blast loaded with No. 6 shot is observed clinically, at 6 feet the wound inflicted is essentially a central blast, whereas at 24 feet the pattern is that the bulk of pellets has begun to spread out concentrically (although they are still contained within a 6-inch circle). For instance, a 12-gauge shotgun loaded with a No. 6 shell gives a muzzle velocity of about 1,300 feet per second and will penetrate a 4-inch thick telephone book when fired from a distance of 12 feet; it will produce a 6 cm defect and will release 2,300 foot-pounds of energy. As noted in a previous discussion on wound ballistics,[1] the ideal antihuman projectile would be one that dissipates all its energy within 15 cm of the point of penetration. At close range, the highly lethal shotgun certainly meets this criterion. As with other firearms, the kinetic energy expended is equal to

$$\frac{\text{mass} \times \text{velocity}^2}{2g}.$$

When one studies the kinetic energy of pellets fired at different ranges, it becomes apparent why shotgun charges and rifle projectiles behave so differently at ranges over a few yards. At a range of 40 yards—a small distance for a high-powered rifle—shotgun pellets would have lost more than half of their original energy. But, at close range an interesting comparison can be made between the 55-grain, 5.56 mm M-16 rifle (used by the United States armed forces in Vietnam) and the 12-gauge shotgun. The M-16 has a muzzle energy of 1,250 foot-pounds, whereas a 12-gauge shotgun with No. 5 shot has an energy of 2,247 foot-pounds. Again, range is the key factor. It can easily be seen why the shotgun is so lethal at close range.

Buckshot—the most common load used by police and military personnel—warrants special comment as well. It was originally designed for use on larger game animals such as deer and its larger mass makes buckshot much more effective at longer ranges. To make this point more clear, consider that each pellet hits the body at a velocity of more than 1,000 feet per second and that each 00 buckshot pellet is about the size of a .22 caliber bullet. Each blast from this type of load, then, contains about nine pellets with an obvious wounding effect.

One additional point should be made concerning the use of magnum shells. Unlike pistol and rifle cartridges, the magnum shotgun shell does not necessarily produce vastly higher velocities. For example, the standard 12-gauge shotgun load has a muzzle velocity of 1,255 feet per second, whereas the so-called "high velocity" 3-inch magnum shell (3-inch denoting the length of the shell) has a muzzle velocity of only 1,315 feet per second. Therefore, very little is actually gained in missile velocity or energy at various ranges by employing magnum shells. What is gained, however, is that a larger load can be discharged. Therefore, the extra powder (that is, magnum) charge is used to propel *more* pellets, not to increase the velocity of the standard load. One can easily tell if a magnum load has been used by examining the spent shell since, with the magnum load, the brass base cup is longer than that of the standard shell.

The clinical characteristics of shotgun wounds are distinctly different from high velocity rifle bullet wounds. In fact, the scope of possible shotgun injuries is so great that only a few general observations can be made.

A person struck by a single pellet which is smaller than BB size is seldom seriously injured unless hit in the eye. As noted previously, most serious human wounds occur at ranges much closer than 20 yards where most of the total pellet charge hits the victim. Again, range is the most important determinant of the amount of damage inflicted by a given shotgun charge. The range can be estimated in about 80 percent of shotgun cases, as can the type of shot used—whether small (like No. 6) or large (like 00 buck).

Wounds made by 00 buck deserve further mention. As noted earlier, each pellet is about the size of a .22 caliber bullet and has a velocity which can exceed 1,000 feet per second.[2] Consequently, each of the pellet wounds should be treated as

separate low-velocity pistol wounds, and more or less independent of range. As might be expected, victims of close range 00 buckshot wounds seldom reach the hospital.

One brief word should be said about rifled slugs. These shells are single projectiles originally designed for killing larger animals and can be fired from any standard shotgun. In relation to the popular 12-gauge weapon, the slug would be 0.730 caliber with a weight of 295 grams; the .357 magnum, in contrast, is about 90 grams. The muzzle energy is 2,480 foot-pounds and these rifled slugs are quite accurate up to about 125 yards. They are huge—approximating those used in buffalo guns of the Wild West days, and they produce tremendous wounds. Human wounds of this type are very rare, but awareness of this injury is the key to successful management. Their wounding characteristics are similar to other medium-velocity (muzzle velocity of 1,800 feet per second) projectiles except that the mass of the bullet is much greater.

Once the approximate range is ascertained, an intelligent approach to wound management can be formulated. Sherman and Parrish[3] have classified shotgun wounds into three categories:

Type I shotgun injuries. These are sustained at long range (greater than 7 yards). This would correspond to an across-the-street injury and such wounds involve penetration of subcutaneous tissue or deep fascia.

Type II shotgun injuries. These are sustained at close range (3 to 7 yards). They correspond to across-the-room range injuries. These types of wounds usually involve structures deep to the fascia.

Type III shotgun injuries. These are sustained at a very close range, that is, less than 3 yards. These wounds usually involve massive tissue destruction and correspond to more or less point-blank range injuries.

Type I injuries usually produce a scatter type wound. At 40 yards, however, a No 6 shot blast has lost most of its energy and thus penetrates minimally to moderate distances (Figure 1). At ranges of 20 yards or more, these small shot may penetrate the abdomen and cause an incredible number of holes in the bowel. Several authors have advocated expectant management of those scatter-type wounds caused by small shot at relatively long distances.[4] The rationale behind use of nasogastric suction and broad spectrum antibiotic therapy rather than immediate operative

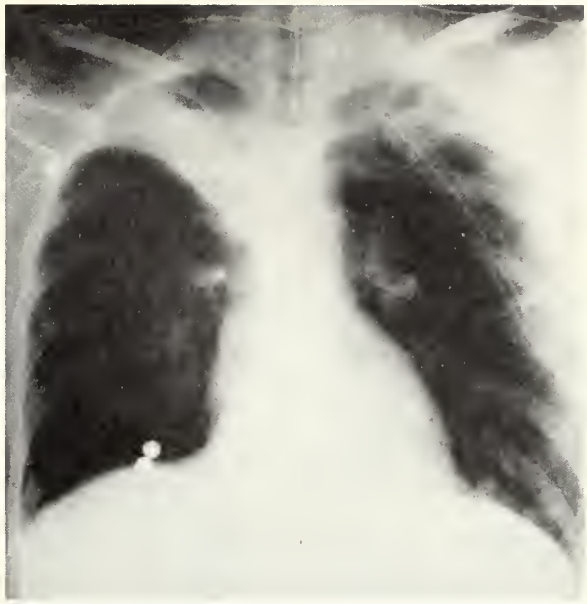

Figure 1.—Roentgenogram showing intrathoracic buckshot.

intervention stems from the fact that these small pellet holes may be enormous in number and the individual holes quite small—often no greater in diameter than a 14-gauge needle. Furthermore, there is usually no outpouching of mucosa and relatively little spillage so that they will often seal —without sequelae. No further generalizations can be made, but the choice of therapy should be made intelligently taking into consideration the range and type of pellets used to inflict the injury as well as the clinical findings. As in the case of all shotgun injuries, tetanus toxoid is prescribed along with admission to hospital for observation. Frequent examinations for evidence of blood vessel or nerve injury of the extremity are also indicated.

Type II wounds cause a tighter pattern of injury and will usually demand a more aggressive approach to management (Figure 2). Injury at this range is usually to structures deep in the fascia and one must be alert to the possibility of vessel injury, nerve injury, and more extensive damage to the bowel than from simple small perforations. The expectant management of abdominal injuries of this type cannot be justified because velocity in this range can be sufficient to cause tangential tears in bowel, and because small groupings of pellets can destroy segments of bowel. Upon exploration, small perforations should be sutured and major areas of bowel injury resected. Injuries to the liver, spleen, stom-

ach, kidney and colon should be managed no differently than any other low-velocity missile wound. Perforation of the aorta and vena cava are usually successfully managed by simple suture. Type II injuries which penetrate the chest can be managed most often by chest-tube drainage. One must be on the alert, however, for cardiac injury with subsequent tamponade and for major vessel injury. Angiography should be used liberally as part of the evaluation process. Esophageal injuries are also a possibility and when mediastinal penetration is likely, esophagrams should be obtained utilizing soluble contrast material. Type II injuries of the head, neck and extremities are managed like any other low-velocity injury but with a high index of suspicion for vascular injury. The incidence of arteriovenous fistula formation post-shotgun injury is quite high. The liberal use of angiography or direct exploration if the index of suspicion is high can help identify these injuries.

Figure 2.—Flat plate roentgenogram of abdomen showing buckshot.

Type III injuries can tax the skills of a multitude of surgical specialists (Figure 3). They usually cause massive local destruction, and hemorrhage is the immediate lethal factor in most cases. Not only pellets, wadding, gunpowder debris and casing debris are blasted into the body, but also other foreign material such as wood (if the victim is behind a door, for example), clothing and skin. Consequently, massive bacterial contamination is the rule, and development of gangrene and necrotizing fasciitis are relatively common. Therefore, almost all of these wounds require extensive debridement and exploration. Repeat exploration or use of second-look procedures to further debride necrotic tissue are often advisable as well. Type III wounds of the chest carry the highest mortality. Chest wall

Figure 3.—External entrance wound showing pronounced tissue destruction of close-range shotgun blast.

defects are common and lobectomy or pneumonectomy are often required for definitive treatment.

The mortality rate for Type I injuries in most reports is low (ranging from 0 to 5 percent), while for Type II injuries it is about 5 percent to 10 percent. Type III gunshot wounds have an associated mortality rate of 15 percent to 20 percent. When one examines the causes of death, the only common denominator is the range from which the missile was fired. Among all types of shotgun injuries, 85 percent to 90 percent of the deaths will be due to Type III injuries, with hemorrhage being the single most common cause of death. In the study by Sherman and Parrish,[3] the average period of survival of those patients dying was 2.3 hours, which emphasizes the importance of prompt, vigorous resuscitation and immediate definitive operation.

In summary, one can most successfully manage shotgun injuries by employing the following general guidelines.

- Carry out prompt and vigorous volume resuscitation.
- Inspect the wounds because, unlike the deceiving high-velocity rifle wound, inspection of the shotgun wound is most informative and is the key to treatment and prognosis.
- Treat all buckshot wounds as if they were multiple low-velocity bullet wounds.
- Use angiography evaluation liberally whenever there is any possibility of vascular injury.
- Explore aggressively all Type II and Type III wounds.
- Debride all devitalized tissue and reoperate, as necessary, to reevaluate any questionably viable tissue.

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Management of Facial Paralysis Due to Temporal Bone Fracture

IT IS VERY IMPORTANT to determine if facial paralysis has been delayed or is immediate. Most delayed paralyses get better by themselves. Most immediate ones do not get better. If immediate, and the nerve is out electrically—not excitable—then explore routinely. When to explore it? On the 21st day. Usually we have to graft the nerve because we have no way in the fallopian canal to mobilize the nerve and get the ends together after we have cut out the bad part. If the nerve has been damaged enough to cause the paralysis, you usually have to graft it. Why the 21st day? The time when the nerve cell body is maximally able to push axoplasm is at three weeks. After that time it descends, until at about one year it reaches almost the asymptote, and ever after that the nerve cell body is less and less able, until finally the nerve cell body degenerates in the brain stem. At one year, almost half the nerve cell bodies in the facial nucleus are gone. They are simply wiped out. . . . If the paralysis is immediate and the nerve retains its excitability—wait. But keep testing. And finally, if the paralysis is immediate or delayed and the nerve loses its excitability—explore.

—BRIAN F. McCABE, MD, *Iowa City, Iowa*

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Refer to: Friedmann CTH: Psychiatry and psychotherapy—Is a divorce imminent? (Commentary). West J Med 129: 156-159, Aug 1978

Psychiatry and Psychotherapy

Is a Divorce Imminent?

CLAUDE T. H. FRIEDMANN, MD, *Torrance, California*

Despite the long tradition of psychiatrists practicing psychotherapy, many psychiatric and medical leaders are predicting and urging a reorientation of psychiatry toward the medical model. They would leave psychotherapy to psychologists, social workers and the like. Many social, governmental and institutional factors favor such a change. The marriage of psychiatry and psychotherapy has always been an uneasy one, and the push for divorce may be irresistible. The author cautions that a divorce could be detrimental to medicine by substituting, in the name of "science," a dehumanized, technological psychiatry for the current "moral" treatment. One alternative to divorce is a broader approach to psychiatry, combining biological, neuromedical, socioenvironmental and psychodynamic factors. The divorce, though imminent, should be resisted.

PSYCHIATRY, the branch of medicine concerned with disorders of the mind, has for many years utilized psychotherapy as a principal treatment tool. This has been especially true in the United States, where Freudian teaching has been popular and the psychodynamic principles derived therefrom widely used. Various types of psychotherapy exist. They share in common interpersonal interaction between a healer and a patient, they pay particular attention to social, environmental and intrapsychic issues, and they utilize techniques such as suggestion, hypnosis and psychoanalysis aimed at the patient's mind. The psychotherapies are distinct from the somatotherapies—such as drugs and electroconvulsive treatment—in which attempts are made to alleviate mental symptoms using the biological and chemical soma.

Psychotherapy has become so much a part of American psychiatry that, for many, the two terms have become almost synonymous. Their modern marriage, begun in the 19th century and brought to fruition by Sigmund Freud, consequently has become a veritable fusion. A great proportion of office and hospital psychiatry involves psychotherapy, and psychotherapy continues to be a major pillar of many training programs. Therefore, the thought of psychiatry divorcing from psychotherapy is foreign to many

Dr. Friedmann is Assistant Professor of Psychiatry, University of California, Los Angeles, School of Medicine, and Head Physician, Adult Psychiatry Crisis and Outpatient Clinic, Harbor General Hospital, Torrance, California.

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Reprint requests to: Claude T. H. Friedmann, MD, Adult Psychiatry Crisis and Outpatient Clinic, Harbor General Hospital, 1000 West Carson St., Torrance, CA 90509.

psychiatrists—if not absurd. Nonetheless, the question of whether or not psychiatrists should continue to learn and carry out psychotherapy is currently a much discussed issue in psychiatric circles. Many in psychiatry are pushing hard for a divorce. Should such a change come about, the results would affect the entire realm of medical practice. Therefore, it behooves us to become familiar with the arguments, pro and con.

The Argument for Divorce

In 1973 L. J. West[1] wrote an article entitled "The Future of Psychiatric Education." In it he predicted that by 1984 most psychotherapy will be done by social workers and psychologists and much of today's office psychiatry by family practitioners and internists. Although he warns against losing the "expertise in psychodynamics accumulated over the past 90 years," he nonetheless sees future psychiatrists as much more of neurologists, endocrinologists and behavioral scientists than their predecessors. West feels that future psychiatrists will also be teachers for, and provide liaison to, many medical and mental health disciplines.

Several economic factors add credence to West's predictions regarding psychotherapy. First, psychiatrists are physicians. As such, they are very expensive. Jerome Frank[2] has pointed out that no type of psychotherapist or psychotherapy has ever been proven better than any other. Therefore, one might ask, because social workers and psychologists generally charge lower fees than psychiatrists, why not send patients to them? Certainly, the planners of national health insurance might feel this way, as might patients unable to afford a psychiatrist's fee. In short, increased governmental and economic pressures, coupled with a growing need within medicine itself for the scientific and medical expertise which only a physician-psychiatrist can give, might well push psychiatry in the direction West predicts.

Bertram Brown,[3] former Director of the National Institute of Mental Health, has written that, in his opinion, the era of the analyst and dynamicist in psychiatry appears to be over and the era of the biological psychiatrist is upon us. Brown asserts that during the past 20 years most advances in the field of psychiatry have been in pharmacology, biology and the treatment of psychoses—not in psychotherapy. The biological psychiatrists, he stated, are the change agents of today's psychiatry. Thomas Hackett,[4] Massachusetts General Hospital's Chairman of Psychiatry, goes a step further: "Unless we are at home in medicine, psychiatry is homeless." He feels that, apart from their medical training, psychiatrists have little more to offer to patients than clergymen, social workers and lay therapists. Psychotherapy is currently fragmented into many factions and schools, and he warns that if psychiatry does not get out of psychotherapy and back into medicine, we are, in his words, "an endangered species."

Eaton and Goldstein[5] have indicated that the functional egalitarianism engendered by multidisciplinary sharing of psychotherapy has blurred the boundaries between psychiatry and the other mental health fields. As a result, perhaps, the general public no longer values the unique entity we call psychiatry. They point out that the result has been a substantial decline over the past ten years in federal dollars available for psychiatric education, as well as a considerable decrease in the percentage of American medical school graduates entering psychiatry. Perhaps, then, Hackett is right. Certainly, many American medical schools have recently seen within their own psychiatry departments a shift away from psychodynamics into biological psychiatry and other nonanalytic fields. Perhaps the leading edge of this change has been the Department of Psychiatry of the Washington University in St. Louis, where research into psychiatric nomenclature has led the American Psychiatric Association to consider sweeping changes in basic psychiatric diagnosis, putting psychiatry more squarely within a medical model: a model, one might add, not dissimilar to European—and, most notably, British—psychiatry. Although the researchers do not necessarily recommend divorce from psychotherapy, changes often go further than the research that began them had envisioned. Consequently, psychiatry, for all the reasons stated above, may indeed be on the brink of divorce from psychotherapy.

The Argument Against Divorce

The marriage between psychiatry and psychotherapy has always been an uneasy one. Descriptive psychiatry, personified by Kraepelin, has often been at odds with dynamic psychiatry, personified by Freud. Psychotherapy is not at all easy to do, because, as Greenblatt[6] has pointed out, it is very difficult for a person to learn how to deal with the deepest feelings of patients. Descriptive psychiatry, in that sense, is much

easier to do, as it places less emotional strain on the therapist. Both Greenblatt[6] and Sederer[7] have traced the roots of "moral" psychotherapy from the French Revolution into mid-19th century America. Without the use of somatic treatment and using only interpersonal, social and environmental therapies, the Worcester State Hospital, leading purveyor of moral treatment, had a 70 percent cure rate. However, in the late 19th century, three factors put a strain on this moral treatment: the rise of scientific neurology and the belief that madness was due to specific brain damage, Darwin's theory which worked against salvaging "the weak," and a huge influx of patients which overwhelmed mental hospitals in the United States.

Sederer[7] finds similarities between late 19th century and current American psychiatry. When overwhelmed by sheer numbers, rising costs and diminishing funds, we may focus on neurology to do *something,* because we no longer have adequate staff to carry out moral treatments. "This type of solution to the pressure of practice has the aura of science . . . that some feel gives psychiatry a medical flavor," he stated. To do psychotherapy, he asserted, one needs warmth, genuineness and empathy, which create a relationship that allows a patient to relate his most intimate feelings and thoughts, something far deeper and requiring more therapeutic skill than that needed to obtain a history and physical examination. He agreed with Greenblatt that moral treatment, psychotherapy, is very hard to do, and felt that the medical model is very seductive, especially to medical students and junior trainees, because it involves much less personal anxiety on a therapist's part. Since biological treatment is cheaper than psychotherapy and places less emphasis on patients' responsibilities to participate in their own cure, and tends to treat patients like infants, biological psychiatry is also easier on all other concerned parties. Therefore, he argued, with more and more Americans demanding psychiatric care, with the increased need for psychiatric consultation within the medical setting, and with the rising cost of health care, the tendency, should psychiatrists ever stop practicing and learning psychotherapy, will be for the separation to perpetuate itself. Once divorced, he feels, these factors will perpetuate a permanent schism.

Sederer asserted that science is a form of humanism, but "scientism," the cult of science that worships technology for its own sake, is unidimensional and antihumanistic. It reduces man to a mechanistic, concrete, nonindividual entity. Quoting Sir William Osler, he stated the following: "'The human heart has a hidden want which science cannot supply.'" He argued forcibly that without psychotherapy psychiatry is "just like the rest of medicine," with nothing unique or special to offer patients. He warns against throwing out psychotherapy the way our 19th century predecessors discarded moral treatment.

Brown[3] pointed out another reason to continue to do psychotherapy: consumerism. He alleged that, as in England, there will always be people who value a physician's ethical tradition and the ability to treat both physical and mental problems. Thus, a demand for psychotherapy by psychiatrists will continue. Strain[8] pointed out that the psychiatrist who consults with his medical colleagues is often asked to deal with emotions, doctor-patient issues, and environmental issues. Without an understanding of psychodynamics and interpersonal interactions, the psychiatrist will be of limited value to his consultees. Dogherty and associates[9] warned that the subject-object relationship between doctor and patient, inherent in the medical model, is very different from the personalized subject-subject relationship of psychotherapy. Put another way, psychotherapy humanizes the patient and accentuates his unique individuality. A schizophrenic, for example, who fears losing his identity, may have his fears realized if in his relationship with his therapist he is treated like an object with a disease who needs pills. In other words, a totally organic approach to the patient will be antitherapeutic and lead to further ego disintegration. To adequately heal even the sickest of psychiatry's patients—the schizophrenics—one needs trust and humanism, in addition to medications. And schizophrenics are one group of patients virtually all prognosticators see as viable clients in psychiatry's future.

Can the Marriage Be Saved?

Eisenberg[10] pointed out that psychiatry is in many ways similar to healing in primitive cultures. The shaman shares many characteristics with the psychiatrist. He stated that medicines alone are generally no cure for psychiatric illness; they merely diminish symptoms. "Brainless psychiatry," he asserted, is as bad as "mindless medicine." Rather than splitting psychiatry's functions by divorcing the biologic from the psyche, he spoke for a fusion in mind-body

relationships. Psychiatry can provide a bridge between soma and psyche, but only if it encompasses both.

Yager[11] feels that human behavior is too complex to be treated from one point of view alone. A psychiatrist, in order to effect the best possible solution to a clinical situation, must know behavioral science, biology, and many types of therapy. Above all, the psychiatrist must be flexible so that he can choose from a variety of therapeutic possibilities. Lesse warned against the worship of "rating scales": over-objectification at the expense of teaching psychotherapy.[12] He feels psychiatry must move to a new level, by interrelating the psychobiological, psychodynamic and psychosocial into a total psychiatry. If this can be done, and if we do not cast off psychotherapy in our zest for neurobiology, the marriage can survive. Psychiatry must expand, not contract. And we in psychiatry must take pains to explain to our medical colleagues that psychotherapy, in tandem with the more "medical" aspects of psychiatry, has much that is unique and important to offer. An eclectic psychiatry, properly applied, can be beneficial to psychiatric and non-psychiatric patients alike.

Is divorce imminent? We must say yes. As Dogherty[9] clearly showed, combining a medical-objective and psychotherapeutic-subjective view of patients is a very difficult task. The pressures for separation are immense. But the benefits to mankind, if the marriage can be saved, are great. If psychiatry broadens, by keeping what it now has and expanding into newer areas, we will all be the better for it. But it will take a lot of work to keep the marriage together. I vote we try.

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Antibiotic Prophylaxis of the Eyelids

THE LID MARGINS are waterproof. They shed tears, as we all know; they are covered with mybomian secretion and they resist antibiotics in an aqueous vehicle. So, for preoperative preparation, one must use an antistaphylococcal ointment.

—HENRY F. ALLEN, MD, *Boston*

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Mitral Valve Prolapse Complicated by Ruptured Chordae Tendineae

JOHN S. CHILD, MD
WILLIAM R. CABEEN, JR., MD
NIGEL K. ROBERTS, MD
Los Angeles

DURING THE LAST DECADE the syndrome of mitral valve prolapse has generated a great deal of interest. Various names for this syndrome include the floppy mitral valve syndrome, the systolic click murmur syndrome and the billowing mitral valve syndrome.

The prevalence of this problem, particularly in young women, may exceed 10 percent.[1] Although most people with this disorder are asymptomatic, many have a variety of symptoms (chest pain, fatigue, dyspnea, palpitations, syncope). The estimated frequency of this problem makes it important that each medical practitioner have some knowledge about techniques of diagnosis, potential complications, and therapeutic recommendations in these patients.

Report of a Case

A 22-year-old woman had been well until the age of 20 when she noted the onset of palpitations and sharp left precordial pains unrelated to exertion. Several emergency room visits without evidence of any abnormal findings prompted one physician to indicate he felt that the problem was "cardiac psychoneurosis."

The patient sought cardiology consultation. Findings on physical examination at that time were within normal limits except for the development of a faint midsystolic click and late systolic murmur (grade II/VI) when the patient was squatting from a standing position. On standing from the squatting position, the murmur became inaudible and the click merged with the first heart sound. Resting 12-lead electrocardiogram, treadmill and x-ray studies of the chest showed no abnormalities. A 24-hour holter monitor recording showed only sinus tachycardia at times when the patient felt the typical palpitations. An M-mode echocardiogram (Figure 1) showed late systolic posterior bowing of the mitral valve typical of mitral prolapse. She was advised to use anti-infective endocarditis precautions during dental and surgical procedures, and was reassured that she should pursue normal activities. No medication was given.

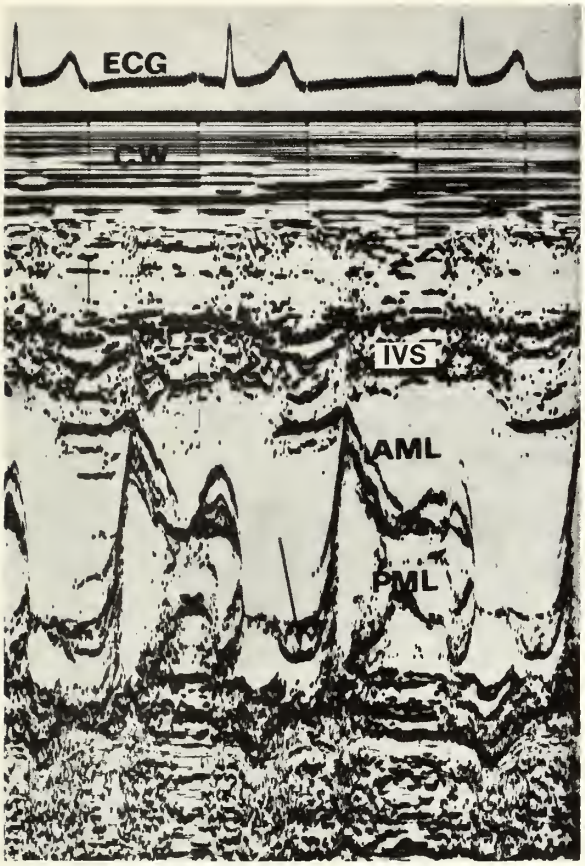
In the next several months, there were no changes in the patient's symptoms but she was more tolerant of them. Then, while doing housework, she noted the sudden onset of moderate shortness of breath which gradually subsided over the rest of that day. The following day, she was again examined, and at that time the systolic murmur was now grade III/VI in intensity, holosystolic, with late systolic accentuation, with radiation to the left upper sternal border and to the axilla. The lungs were clear. No abnormal jugular venous distension was detected. A repeat echocardiogram gave findings consistent with a flail portion of the mitral valve, as might occur with ruptured chordae tendineae: (1) coarse chaotic diastolic flutter of the apparent posterior mitral leaflet (Figure 2), (2) systolic flutter of the mitral closure line and (3) systolic mitral prolapse into the left atrium (Figure 3) beyond that which is usually seen in the mitral prolapse syndrome. Blood cultures were negative. No therapy was required and the patient's condition has remained stable during subsequent follow-up examinations.

Discussion

The mitral leaflets, chordae tendineae and annulus may all be affected by myxomatous degeneration which results in systolic prolapse of the redundant leaflets into the left atrium. In most patients, the cause of these changes is unknown, although the syndrome has been seen in association with Marfan syndrome, Ehlers-Danlos syn-

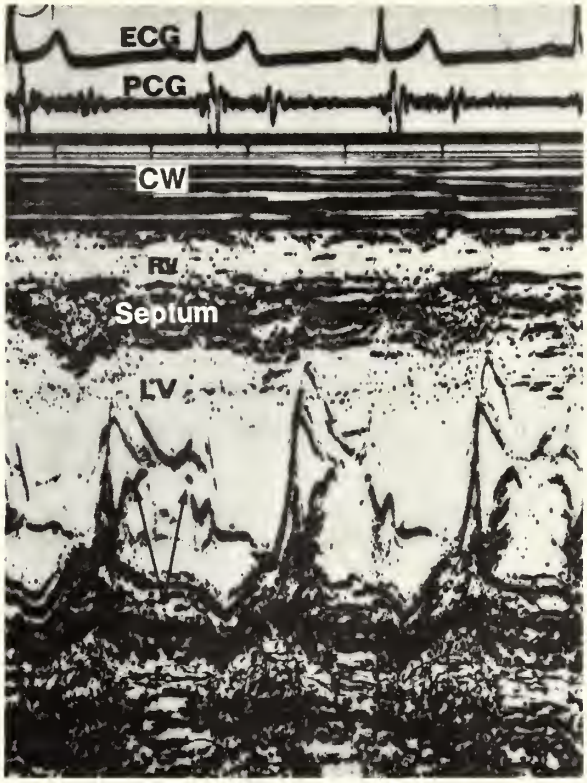
From the Divisions of Cardiology, Departments of Medicine and Pediatrics, University of California, Los Angeles, School of Medicine.

Reprint requests to: John S. Child, MD, Division of Cardiology, Department of Medicine, UCLA School of Medicine, 10833 Le Conte Avenue, Los Angeles CA 90024.



AML = anterior mitral leaflet
ECG = electrocardiogram
PML = posterior mitral leaflet
CW = chest wall
IVS = interventricular septum

Figure 1.—Unretouched baseline M-mode echocardiogram showing the mitral valve with late systolic prolapse **(arrow).** This is the classic pattern.



ECG = electrocardiogram
PCG = phonocardiogram
RV = right ventricle
CW = chest wall
LV = left ventricle

Figure 2.—Echocardiogram done after onset of acute shortness of breath. The arrows indicate the chaotic anterior diastolic motion of the posterior mitral leaflet. This pattern is consistent with rupture of chordae tendineae.

drome, atrial septal defect and ischemic heart disease.[2] It is observed more often in young women, but may be seen in children or in the elderly.

Most people with this syndrome are asymptomatic. However, a small percentage report a variety of symptoms. Chest pain usually is unlike angina in quality or location, is unrelated to exertion and is unrelieved by therapy with nitroglycerin. However, the chest pain may at times be indistinguishable from angina pectoris. Fatigue and dyspnea are frequent. Because there is often normal exercise tolerance, these patients are often thought to have psychoneurotic symptoms. Many patients complain of palpitations. Continuous ambulatory electrocardiography has shown a variety of arrhythmias (atrial and ventricular premature depolarizations or tachyarrhythmias), but often there is a poor correlation between symptoms and arrhythmias detected.

Physical examination usually provides the diagnosis. General appearance is often normal, but asthenic habitus and thoracic bony abnormalities (loss of thoracic hypnosis, pectus excavatum, scoliosis) are common. Auscultatory signs are the hallmark. The systolic click and late systolic murmur may be quite variable in presence or timing but may be detected more easily by bedside use of physiologic maneuvers. The typical click is early or midsystolic, followed by a decrescendo murmur which lasts to the second heart sound. On occasion the murmur may be holosystolic. The clicks are due to sudden tensing of chordae tendineae and tethering the billowing mitral valve, much as might be heard as a sail snaps to the end of its rope when suddenly filled with wind. The mitral regurgitation murmur occurs if prolapse is sufficient to disrupt normal leaflet apposition.

By altering ventricular volume and shape, physiologic postural maneuvers secondarily affect

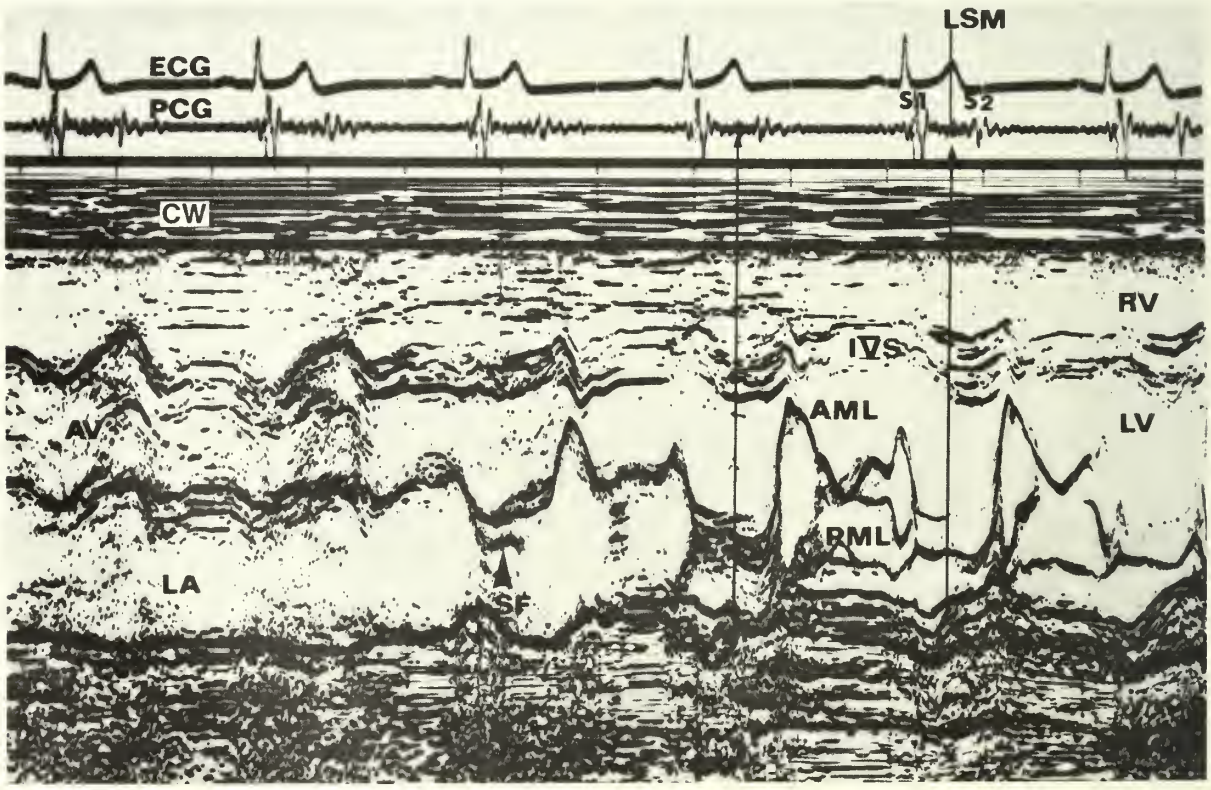
the onset and degree of prolapse.[3] Loudness of the murmur is affected also by the effects of these maneuvers on left ventricular systolic pressure. If no murmur is heard in the supine position, one can often be provoked by sitting or standing, whereupon the systolic click is heard earlier, at times merging with the first sound. Prompt squatting moves the click later in systole, toward the second sound, and delays the onset of the murmur, but may intensify it (refer to Figure 5, reference 2).

Numerous nonspecific electrocardiographic abnormalities have been reported[2] including inverted T-waves, ST segment depression, prolonged QT interval, and conduction abnormalities. Exercise stress testing often elicits arrhythmias, and may show "false-positive" ischemic ST segment changes.

Echocardiography has become an important, safe, noninvasive tool for diagnosis. Approximately 20 percent of patients with clinical findings of mitral prolapse are missed by the technique, however. The key pattern is an abrupt systolic posterior motion of one or both of the mitral valve leaflets (Figure 1). A second pattern is pansystolic posterior bowing of the systolic closure line. In addition, the effects of mitral regurgitation on the heart can be assessed (left atrial and ventricular size), thereby allowing some estimate of its severity and chronicity.

The four major complications include sudden death, infective endocarditis, spontaneous rupture of chordae tendineae and progressive mitral regurgitation.[2,4,5] Sudden death is a rare but real concern and may be due to arrhythmias. The risk of endocarditis is an indication for antibiotic prophylaxis during dental and surgical procedures using the recommendations of the American Heart Association.[4-6] Endocarditis may occur in persons with isolated systolic clicks as well as those with late systolic murmurs.[2]

Spontaneous chordal rupture, as in our patient, is probably due to the excessive tension imparted to weak chordae tendineae (myxomatous changes)



AML = anterior mitral leaflet
AV = aortic valve
CW = chest wall
ECG = electrocardiogram
IVS = interventricular septum
LV = left ventricle
PML = posterior mitral leaflet
RV = right ventricle

Figure 3.—Standard echocardiographic sweep from aorta to left ventricle. The arrowhead indicates the systolic flutter (SF) of the mitral valve as seen in the left atrial (LA) cavity consistent with a flail portion of the mitral valve. The phonocardiogram (PCG) shows the heart sounds (S_1,S_2) and the systolic murmur with late systolic accentuation (LSM).

by the billowing mitral leaflet. This can also be secondary to endocarditis. The patient may fit into a wide clinical spectrum ranging from no symptoms to acute pulmonary edema. Either chordal rupture, endocarditis, or gradual progression of the underlying myxomatous process may result in severe mitral regurgitation in a small number of patients, and consequently require operative intervention.

The case discussed here includes many of the features reported in mitral prolapse syndrome: palpitations, atypical anginal chest pains, fatigue, systolic click and murmur during squatting, and classic echocardiographic findings. One of the complications, namely, spontaneous rupture of a mitral chorda tendinea with mild symptoms that promptly resolved was seen in the patient.

Key points to remember are (1) the utility of the physiologic postural maneuvers in auscultation, (2) the uscfulness of echocardiography in diagnosis and (3) recommendations to the patient are needed for anti-infective endocarditis prophylaxis. Propranolol (Inderal®) at present is the primary drug used in therapy of the arrhythmias, and can be of use in the management of chest pain.

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Biology and Treatment of Micrometastases in Approach to Breast Cancer

THE PRESENCE of distant metastases is the most common cause of death in patients with breast cancer. Yet, when the disease presents clinically, it appears to be localized in more than 70 percent of the patients. The use of a more extended or more radical surgical procedure or the addition of radiotherapy has not improved the survival rate. In other words, treating breast cancer as a local disease has not made a major impact. Involvement of the lymph nodes indicates a very poor prognosis. Of those patients in whom there are positive lymph nodes, 75 percent will be dead of their disease within ten years; if more than three nodes are involved, then the mortality goes up to 90 percent.

Chemotherapy is most effective against tumors that are small in volume or rapidly growing. Resistance to chemotherapy is a function of a low growth rate in a high-cell number. In general, chemotherapy is less effective against visible tumor masses than it is against the micrometastases and, in certain experimental situations, surgical operation alone may not be effective; chemotherapy alone is not effective, but the combination may be much better in the treatment. Most of chemotherapy up until recently has been restricted to use in patients with high volume, low-growth rate disease. And reserving chemotherapy for that end-stage patient has not increased the cure rate.

—PAUL P. CARBONE, MD, *Madison, Wisconsin*

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Medical Information

Analgesic Hepatotoxicity

RICHARD R. BABB, MD
Palo Alto, California

OVER THE PAST FEW YEARS it has become clear that salicylates (the most popular being aspirin) and acetaminophen, both widely used over-the-counter analgesics, can lead to hepatotoxicity.[1-11]

Although the ingestion of aspirin by healthy volunteers may cause a slight increase in serum transaminases,[5,12] this is very uncommon in clinical practice.[13] However, when aspirin is given to patients with connective tissue disorders, such as juvenile and adult rheumatoid arthritis,[1,6-8] disseminated lupus erythematosus[2,3,5] and rheumatic fever,[14,15] direct hepatocellular damage may ensue. In general, the toxic effect occurs when the blood salicylate level is greater than 25 mg per dl,[1,3,15] although this correlation is not an exact one.[7,8] In most of the reported cases, the patients have complained of mild symptoms, and serum transaminases have risen 2 to 50 times above normal. When the salicylate therapy is stopped, the patients have quickly improved, and results of liver function tests have returned to normal. Drug rechallenge has led to a return of clinical abnormalities. On liver biopsy specimens, portal and lobular inflammation is seen.

Unless the above is remembered, patients with disseminated lupus erythematosus and abnormal findings on liver function tests may receive the mistaken diagnosis of "lupoid" or chronic active hepatitis rather than aspirin-induced hepatotoxicity.[2] In a retrospective analysis of 19 such patients, Seaman and Plotz noted 14 to be receiving aspirin therapy, and the conditions of all improved when the administration of the drug was stopped.[5]

Acetaminophen is marketed in more than 200 formulations.[16] When taken in massive doses at one time (at least 10 grams), liver necrosis, coma and death may occur.[17,18] Not so well appreciated, however, are the recent reports of liver damage associated with the *chronic* use of acetaminophen.[9,10] One patient took 3 grams a day for one year, and the others 5 to 8 grams a day for a few weeks. Results of liver function tests, especially of the transaminases, were abnormal, and biopsy findings included both acute and chronic inflammation. Withdrawal of the drug led to clinical improvement, and rechallenge to exacerbation of the laboratory abnormalities. These patients may have been particularly susceptible by virtue of precxisting liver disease, alcoholism and cachexia. Two patients with infectious mononucleosis were observed to have severe liver dysfunction while taking acetaminophen in a dose of 3.6 grams per day.[19]

Normally, acetaminophen is conjugated in the liver with glucuronide or sulfate. Another minor pathway (the cytochrome p-450-dependent, mixed oxidase enzyme system) converts the drug to a metabolite which is then rendered nontoxic by conjugation with glutathionine. Excessive amounts of acetaminophen may saturate the usual metabolic pathways, and as the excess drug is processed by the cytochrome p-450 enzyme system, glutathionine is depleted, and increased amounts of the nonconjugated and, therefore, hepatotoxic, metabolite occur.[16] Ingestion of inducers of the cytochrome p-450 enzymes such as phenobarbital[20] before taking acetaminophen can also lead to increased amounts of the toxic metabolite and thereby potentiate liver damage.[21]

Based on the above, one may conclude the following:

- Under certain conditions, salicylates and acetaminophen are hepatotoxic.
- Patients with abnormal liver function should be questioned closely about the chronic use of over-the-counter analgesics.
- Patients with chronic liver disease or connective tissue disorders should be watched carefully for the development of hepatotoxicity if given salicylates or acetaminophen. If this occurs, the drug should be stopped.

From the Gastroenterology Section, Palo Alto Medical Clinic, Palo Alto, California.

Reprint requests to: Richard R. Babb, MD, Section of Gastroenterology, Palo Alto Medical Clinic, 300 Homer Avenue, Palo Alto, CA 94301.

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Medical Information

Serum Thyroid Hormones in Patients on Replacement or Suppressive Doses of L-Thyroxine

SIDNEY ROSENBLATT, MD
JEROME M. HERSHMAN, MD
Los Angeles

ABBREVIATIONS USED IN TEXT

T_3 = triiodothyronine
T_4 = L-thyroxine
TSH = thyroid-stimulating hormone

CHANGES IN THE normal circulating levels of thyroid hormones occur in patients taking replacement or suppressive doses of L-thyroxine (T_4). Most of the circulating pool of triiodothyronine (T_3) is derived from peripheral monodeiodination of thyroxine.[1-3] Adequate treatment with L-thyroxine usually produces serum T_4 levels similar to or slightly higher than control values, T_3 levels are often slightly lower than controls, and the T_4/T_3 ratio would be expected to be higher than control values. We measured serum concentrations of T_4, T_3 and thyroid-stimulating hormone (TSH) in patients with a variety of thyroid disorders to assess the significance of changes in circulating thyroid hormone levels in patients taking L-thyroxine.

Methods

A retrospective analysis was made of 132 patients receiving adequate suppressive or replacement doses of L-thyroxine. A total of 71 patients were in the hypothyroid group, and 61 were in the euthyroid group being treated for nodular or diffuse goiter. Patients with autonomously functioning nodular goiters were not included. The dose range was 0.1 to 0.3 mg of L-thyroxine, and adequate treatment was assessed by normal concentrations of serum thyrotropin (less than 5 μU/per ml) in all patients without pituitary disease. The patients with pituitary disease all had normal levels of serum T_3 and T_4. Serum T_3, T_4 and TSH were measured by radioimmunoassays.[4] All patients were receiving therapy for at least three months. The patients were otherwise

From the Endocrinology Section, VA Wadsworth Medical Center, Los Angeles, and the Department of Medicine, University of California, Los Angeles, School of Medicine.

Supported by the Medical Research Service of the Veterans Administration.

Reprint requests to Sidney Rosenblatt, MD, Endocrinology Section, Wadsworth VA Hospital, Wilshire and Sawtelle Blvds., Los Angeles, CA 90073.

healthy which excluded non-thyroidal alterations in serum thyroid hormones.

A total of 161 patients without thyroid disease served as normal controls. The age patterns in the controls and treated groups were similar. Statistical significance was determined by Student's t-test.

Results

Table 1 shows the serum T_3, T_4, T_4/T_3 ratio and TSH in the control group and the groups treated with various doses of L-thyroxine. Serum T_4 concentrations and the T_4/T_3 ratio were higher in all the treatment groups irrespective of dose ($p<0.05$). Serum T_3 concentrations were elevated significantly only in the euthyroid treated patients. Serum TSH was undetectable (less than 0.3 μU/per ml) in 58 percent of all patients treated for primary hypothyroidism and 72 percent of all patients in the euthyroid treated group.

When patients in both treatment groups were selected because their serum T_4 was in the lower half of the normal range (5 to 8.5 μg per dl), the T_4/T_3 ratio was 51.4 in the hypothyroid and 48.0 in the euthyroid treated groups. These values were similar to the ratio in untreated controls. The mean T_3 level was 143±29 ng per dl in the hypothyroid treated groups and 150±26 ng per dl in the euthyroid treated groups, which are similar to T_3 concentrations in controls.

Discussion

The data show that T_4 concentrations and the T_4/T_3 ratio in patients receiving replacement or suppressive doses of L-thyroxine are increased. T_3 levels are normal or increased. Higher levels of thyroid hormones were observed in patients treated for goiter suppression because the therapeutic goal was suppression of endogenous TSH secretion.

In patients taking the usually prescribed doses of L-thyroxine, the T_4/T_3 ratio may be altered for two reasons. Firstly, the serum T_4 level is elevated, suggesting that these doses of L-thyroxine are too high. The mean T_4 level in the hypothyroid group was 2.6 μg per dl higher than the mean control value of 7.6 μg per dl, and the mean T_4 value in the euthyroid group was 3.7 μg per dl higher than the controls. To further elucidate this point, we selected those patients receiving therapy who had T_4 levels between 5 and 8.5 μg per dl. Their T_3 levels and T_4/T_3 ratios were unchanged from those of controls. Therefore, the alterations in thyroid hormone relationships is primarily affected by the serum T_4 level. Second, the circulating levels of T_3 in patients taking L-thyroxine is derived primarily from peripheral monodeiodination.[1-3] The reduced thyroidal contribution of T_3, secondary to suppression or loss of thyroid secretion, probably also plays a role.

TABLE 1.—*Serum Thyroid Hormone Concentrations (Mean ± S.D.)*

GROUP	*T_4 dose mg*	*No.*	*T_4 µg/dl*	*T_3 ng/dl*	*T_4/T_3*	*TSH µU/ml*	*Undetectable TSH (Percent)*
Normal	0	161	7.6 ±1.6	153.7 ± 32.7	50.8 ± 13.1	1.8 ± 1.6	4.3
Hypothyroid	0.1-0.15	34	9.2* ± 2.4	168.8 ± 64.4	59.4* ± 23.2	1.3* ± 1.6	44‡
Hypothyroid	0.2	27	11.3† ± 4.6	173.6 ± 44.0	64.3* ± 17.1	1.1* ± 2.3	66‡
Hypothyroid	0.25-0.30	10	10.6† ± 3.4	175.1 ± 22.2	59.3* ± 12.3	0.3† ± 0.8	89‡
Euthyroid	0.1-0.15	11	10.0† ± 3.2	173.7* ± 64.8	59.7* ± 13.2	0.5† ± 0.8	63
Euthyroid	0.20	34	11.1† ± 3.3	181.5* ± 45.5	63.2* ± 15.0	0.4† ± 0.7	71
Euthyroid	0.25-0.30	16	12.7† ± 3.0	186.3* ± 49.0	70.1* ± 14.5	0.1† ± 0.2	81
All hypothyroid		71	10.2† ± 3.5	171.5 ± 52.4	61.2* ± 19.7	1.1* ± 2.1	58
All euthyroid		61	11.3† ± 3.3	181.4* ± 49.5	64.4* ± 14.8	0.3† ± 0.6	72

T_3 = triiodothyronine T_4 = L-thyroxine TSH = thyroid-stimulating hormone

*$P<0.05$ compared with normal untreated subjects
†$P<0.005$
‡Patients with primary hypothyroidism only

By using a sensitive radioimmunoassay for TSH, we showed that most patients taking L-thyroxine had undetectable levels. Nearly all normal and untreated euthyroid goitrous patients have detectable circulating levels of TSH with this assay. We agree with Stock and co-workers[5] that the current textbook recommendations for replacement therapy with L-thyroxine are too high. We recommend 0.1 to 0.2 mg of L-thyroxine for replacement therapy. Suppression therapy with this dose range will effectively reduce TSH to undetectable levels in most patients; however, the dose must be individually tailored for each patient.

Summary

Serum thyroid hormones were measured in patients taking L-thyroxine for replacement or suppressive therapy. Their serum T_4 levels and T_4/T_3 ratios were greater than controls and their serum T_3 levels were normal or slightly increased. This finding was more evident in the euthyroid goitrous group because higher doses of thyroxine were used to suppress TSH secretion. Serum TSH levels were suppressed to undetectable levels in most patients. Replacement therapy for hypothyroidism can be achieved with 0.1 to 0.2 mg of L-thyroxine which will suppress serum TSH to undetectable levels in most patients.

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in memoriam

ALEXANDER, HARRY H., JR., Los Angeles. Died May 15, 1978 in Los Angeles of carcinoma of the pancreas and colon, aged 73. Graduate of Indiana University School of Medicine, Bloomington-Indianapolis, 1929. Licensed in California in 1931. Dr. Alexander was a retired member of the Los Angeles County Medical Association.

ALLEN, HOWARD H., Los Angeles. Died January 29, 1978 in Inglewood of cardiac arrest, aged 75. Graduate of Howard University College of Medicine, Washington, DC, 1928. Licensed in California in 1929. Dr. Allen was a member of the Los Angeles County Medical Association.

BATES, CHARLES E. H., San Francisco. Died June 17, 1978 in San Francisco, aged 83. Graduate of Cornell University Medical College, New York, 1924. Licensed in California in 1926. Dr. Bates was a retired member of the San Francisco Medical Society.

BURNS, MELTON B., Pasadena. Died June 8, 1978, aged 77. Graduate of the University of Illinois College of Medicine, Chicago, 1927. Licensed in California in 1935. Dr. Burns was a member of the Los Angeles County Medical Association

CLEGG, COURTNEY G., San Francisco. Died May 13, 1978, aged 76. Graduate of the University of California Medical School, Berkeley-San Francisco, 1928. Licensed in California in 1928. Dr. Clegg was an associate member of the San Francisco Medical Society.

DUBROW, JAMES L., Los Angeles. Died January 22, 1978, aged 83. Graduate of Georgetown University School of Medicine, Washington, DC, 1922. Licensed in California in 1943. Dr. Dubrow was a member of the Los Angeles County Medical Association.

EVANS, WILLIAM D., Loma Linda. Died February 19, 1978 in Loma Linda of diabetes mellitus, aged 67. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1939. Licensed in California in 1939. Dr. Evans was a retired member of the Los Angeles County Medical Association.

FALCONER, FAY HARVEY, Glendale. Died February 19, 1978 of heart disease, aged 84. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1924. Licensed in California in 1924. Dr. Falconer was a member of the Los Angeles County Medical Association.

FOX, NORMAN C., San Bruno. Died May 8, 1978, aged 66. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1936. Licensed in California in 1936. Dr. Fox was a retired member of the San Mateo County Medical Society.

FULLER, LELAND J., Sacramento. Died April 10, 1978 in Sacramento of liver disease, aged 54. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1949. Licensed in California in 1949. Dr. Fuller was a member of the Los Angeles County Medical Association.

GODSHALL, LEON D., Los Angeles. Died April 12, 1978 in Los Angeles of metastatic carcinoma, aged 83. Graduate of the College of Physicians and Surgeons, Medical Department, University of Southern California, Los Angeles, 1919. Licensed in California in 1919. Dr. Godshall was a member of the Los Angeles County Medical Association.

GOLD, RUBIN L. San Francisco. Died June 3, 1978 in San Francisco, aged 70. Graduate of the University of California Medical School, Berkeley-San Francisco, 1936. Licensed in California in 1936. Dr. Gold was a member of the San Francisco Medical Society.

HARTMAN, SHERMAN W., Encino. Died April 17, 1978 in Encino of multiple myeloma, aged 55. Graduate of Harvard Medical School, Boston, 1949. Licensed in California in 1952. Dr. Hartman was a member of the Los Angeles County Medical Association.

JOHNSON, BYRUM E., Wilmington. Died June 9, 1978 in San Pedro of massive hemorrhage, aged 71. Graduate of Rush Medical College, Chicago, 1939. Licensed in California in 1946. Dr. Johnson was a member of the Los Angeles County Medical Association.

MORRISON, ALAN F., Stockton. Died April 21, 1978, aged 65. Graduate of McGill University Faculty of Medicine, Montreal, 1939. Licensed in California in 1941. Dr. Morrison was a member of the Stanislaus Medical Society.

NELSON, H. BRISTOL, San Francisco. Died May 30, 1978 in San Francisco, aged 77. Graduate of Harvard Medical School, Boston, 1927. Licensed in California in 1952. Dr. Nelson was a member of the San Francisco Medical Society.

NEUMAYR, GEORGE H., San Francisco. Died April 11, 1978, aged 89. Graduate of Rush Medical College, Chicago, 1928. Licensed in California in 1941. Dr. Neumayr was a member of the San Francisco Medical Society.

NOALL, ELMER T., Santa Rosa. Died May 23, 1978 in Santa Rosa, aged 84. Graduate of Rush Medical College, Chicago, 1930. Licensed in California in 1930. Dr. Noall was a retired member of the Sonoma County Medical Association.

WU, JACKSON S., La Jolla. Died May 8, 1978, aged 55. Graduate of West China Union University School of Medicine, Chengtu, Szechwan, 1949. Licensed in California in 1956. Dr. Wu was a member of the San Diego County Medical Society.

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References: 1. Johnson JE: Urinary tract infections, chap. 24, in *Clinical Concepts of Infectious Diseases*, edited by Cluff LE and Johnson JE. Baltimore, The Williams & Wilkins Co., 1972, p. 273.
2. Data on file, Hoffmann-La Roche Inc., Nutley, New Jersey 07110.

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BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

ANESTHESIA IN OBSTETRICS—Maternal, Fetal and Neonatal Aspects—George A. Albright, MD, Assistant of Anesthesia, Stanford University School of Medicine, Stanford, CA. Addison-Wesley Publishing Company—Medical Nursing Division. The Benjamin/Cummings Publishing Company, 2727 Sand Hill Road, Menlo Park, CA (94025), 1978. 480 pages, $42.00.

BLOOD SUBSTITUTES AND PLASMA EXPANDERS—Volume 19 in the series: PROGRESS IN CLINICAL AND BIOLOGICAL RESEARCH—Editors: G. A. Jamieson, PhD, DSc, Research Director, The American National Red Cross Blood Program, and Adjunct Professor, Schools of Medicine and Dentistry, Georgetown University; and Tibor J. Greenwalt, MD, Director, The American National Red Cross Blood Program and Clinical Professor of Medicine, School of Medicine, George Washington University. Alan R. Liss, Inc., 150 Fifth Avenue, New York City (10011), 1978. 354 pages, $36.00 (available in Europe, UK and the Middle East exclusively from European Book Service, Hogeweyselaan 119, WEESP, The Netherlands, price: 108.00 Dutch Guilders).

CLINICAL ANATOMY OF THE HEART—Robert Walmsley, MD, DSc, FRCPE, FRCS Ed, FRSE, Emeritus Professor of Anatomy, University of St. Andrews, Scotland; and Hamish Watson, TD, MD, FRCPE, FRCP, FAAC, Chairman, Section of Cardiology, Department of Medicine, Postgraduate Dean and Director of Postgraduate Medical Education, University of Dundee; Consultant Cardiologist, Tayside Area, Scotland. Churchill Livingstone-Medical Division of Longman Inc., 19 West 44th St., New York City (10036), 1978. 230 pages, $49.50.

COMPUTERS FOR THE PHYSICIAN'S OFFICE—Volume II in the MEDICAL COMPUTING Series—Joan Zimmerman, D Phil, Biomedical Computer Laboratory, Washington University, St. Louis; and Alan Rector, MD, Health Services Research Group, University of Nottingham. Research Studies Press, P.O. Box 92, Forest Grove, OR (97116), 1978. 302 pages, $21.50.

CURRENT OBSTETRIC & GYNECOLOGIC DIAGNOSIS & TREATMENT—Second Edition—Ralph C. Benson, MD, Clinical Professor and Emeritus Chairman, Department of Obstetrics & Gynecology, University of Oregon Health Sciences Center, Portland; and Associate Authors. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1978. 976 pages, $18.00.

GESTATIONAL AGE OF THE NEWBORN—Lilly M. S. Dubowitz, MD, DCH, and Victor Dubowitz, MD, PhD, FRCP, DCH, Department of Paediatrics and Neonatal Medicine, Institute of Child Health, Hammersmith Hospital, Royal Postgraduate Medical School, London. The Benjamin/Cummings Publishing Company, 2727 Sand Hill Road, Menlo Park, CA (94025), 1977. 139 pages, $18.95.

MEASURING MEDICAL EDUCATION—The Tests and the Experience of the National Board of Medical Examiners—Second Edition—John P. Hubbard, MD, President Emeritus, National Board of Medical Examiners; Professor Emeritus, University of Pennsylvania School of Medicine; with chapters by members of the staff, National Board of Medical Examiners: Barbara J. Andrew, PhD, Director, Department of Research and Development; Robert A. Chase, MD, President, November 1974 to July 1977; and Charles F. Schumacher, PhD, Director, Department of Psychometrics. Lea & Febiger, 600 South Washington Square, Philadelphia (19106), 1978. 187 pages, illustrated (plates in color), $12.00.

MEDICINE AND THE REIGN OF TECHNOLOGY—Stanley Joel Reiser, Assistant Professor and Director, Program in the History of Medicine, Harvard Medical School, and Clinical Associate in Medicine, Massachusetts General Hospital, Boston. Cambridge University Press, 32 East 57th Street, New York City (10022), 1978. 317 pages, $14.95.

METABOLISM OF VOLATILE ANESTHETICS—Implications for Toxicity—Ellis N. Cohen, MD, Professor of Anesthesia, Stanford University; Russell A. Van Dyke, PhD, Associate Professor of Biochemistry, Mayo Medical School; with a contribution by James R. Trudell, PhD, Assistant Professor of Chemistry in Anesthesia, Stanford University. The Benjamin/Cummings Publishing Co., 2727 Sand Hill Road, Menlo Park, CA (94025), 1977. 248 pages, $21.95.

OUTLINE OF FRACTURES—Seventh Edition—John Crawford Adams, MD (London), MS (London), FRCS (England), Consultant Orthopaedic Surgeon, St. Mary's Hospital, London; Civil Consultant in Orthopaedic Surgery, Royal Air Force; Production Editor, Journal of Bone and Joint Surgery. Churchill Livingstone—Medical Division of Longman Inc., 19 West 44th Street, New York City (10036), 1978. 320 pages, $13.50.

PAIN—New Perspectives in Measurement and Management—Edited by A. W. Harcus, MB, ChB, DObstRCOG, Head of Medical Affairs, Pharmaceutical Division, Reckitt & Colman; R. B. Smith, BSc, MB, ChB, MD, DipPharmMed, International Development and Medical Director, Pharmaceutical Division, Reckitt & Colman; B. A. Whittle, BPharm, FPS, MSc, PhD, Head of Regulatory Affairs, Pharmaceutical Division, Reckitt & Colman; Foreword by G. V. R. Born, FRCP, FRS, Shield Professor of Pharmacology, University of Cambridge. Churchill Livingstone—Medical Division, Longman Inc., 19 West 44th St., New York City (10036), 1978. 194 pages, $23.50.

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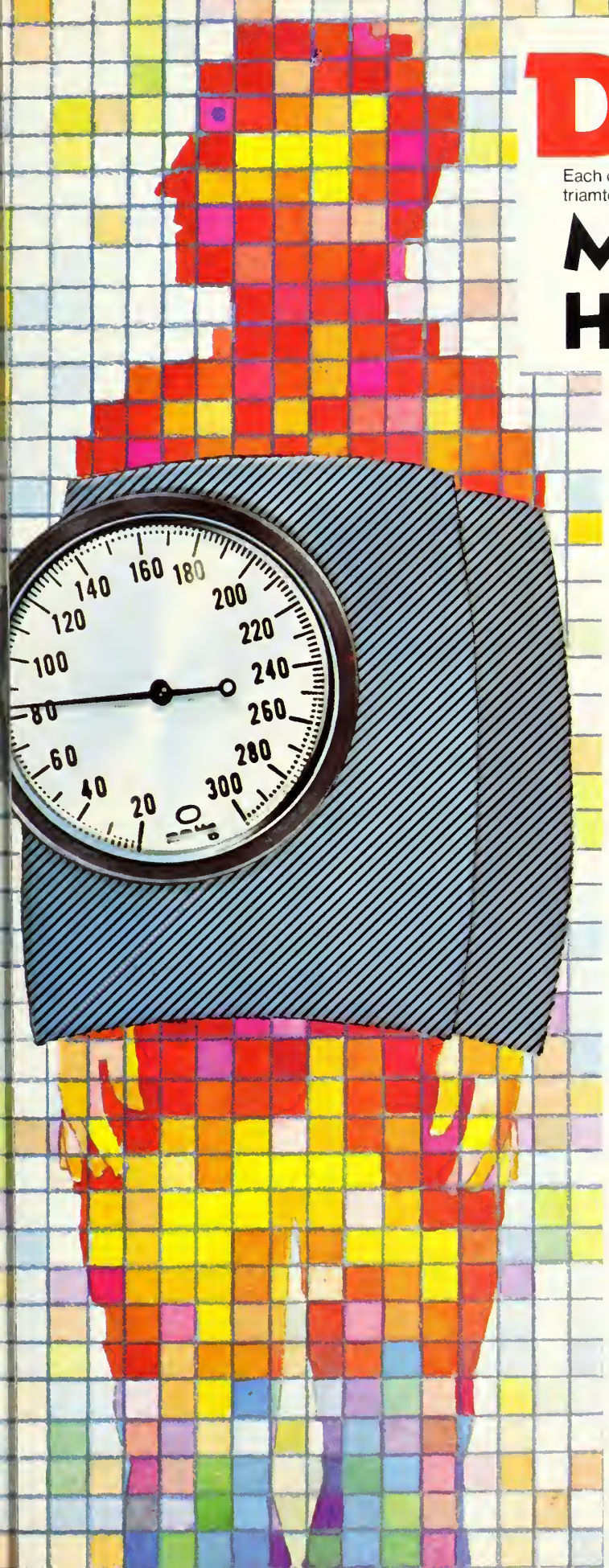

Dyazide®

Each capsule contains 50 mg. of Dyrenium* (brand of triamterene) and 25 mg. of hydrochlorothiazide.

Makes Sense in Hypertension*

Before prescribing, see complete prescribing information in SK&F Co. literature or *PDR*. A brief summary follows:

* **Warning**
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K+ frequently; both can cause K+ retention and elevated serum K+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

Supplied: Bottles of 100 and 1000 capsules; Single Unit Packages of 100 (intended for institutional use only).

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20/20

The first 20 days

- Catapres lowers blood pressure promptly.
- No contraindications.
- Some patients may have dry mouth, drowsiness, and sedation. Tell them that these tend to diminish with continued use.
- Giving the larger part of the divided dose at bedtime can help alleviate drowsiness and sedation.

The next 20 years*

- Lowered blood pressure.
- Little impotence, depression or postural hypotension.
- No fatal hepatotoxicity in over a decade of worldwide use.
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*Tolerance may develop in some patients, necessitating a reevaluation of therapy.

For full details on adverse reactions, warnings, and precautions, see brief summary of the prescribing information on last page of this advertisement.

Catapres® (clonidine HCl)
For Step 2 in
Hypertension

HYPERTENSION

A New Vision of Catapres® (clonidine HCl)

Tablets of 0.1 and 0.2 mg

What you do the first 20 days Can help him the next 20 years

Catapres®
(clonidine hydrochloride)
Tablets of 0.1 mg and 0.2 mg

Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potency. It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established.) These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone, and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase, congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres (clonidine hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all effects of Catapres (clonidine hydrochloride) overdosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100 and 1000.

For complete details, please see full prescribing information.

Under license from Boehringer Ingelheim GmbH

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When the pill, the IUD, or the diaphragm is not the answer.

Now there's Semicid.™

The alternative in non-systemic contraception.

New Semicid (nonoxynol-9) Vaginal Contraceptive Suppository solves many problems of modern birth control alternatives: the pill can have systemic side effects, the IUD may cause discomfort and side effects, the diaphragm is often inconvenient. The fuss and mess of foams, creams and jellies, plus the minor irritations sometimes caused by the other vaginal suppository often discourage compliance.

Now there's a sensible alternative: Semicid. It's a medically tested, non-hormonal vaginal suppository that is both safe and effective. In fact, Semicid contains the maximum recommended 100 mg. level of nonoxynol-9, the long-recognized standard of spermicidal efficacy.

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In a recent U.S. clinical study,* 326 women were monitored for a total of 4890 women-months. This study was conducted by a gynecologist and was carefully reviewed by independent gynecological groups at two major universities. In comparing the findings of these groups with published reports of other contraceptive methods, Semicid is shown to be effective in the prevention of pregnancy.

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Simple and Gentle Enough To Assure Compliance.

Semicid delivers this potent spermicide in a convenient, gadget-free, one-inch vaginal suppository that maximizes compliance. Your patient can use it simply, unobtrusively, and only when it is needed. Once it is digitally inserted, Semicid forms an effective spermicidal barrier within 15 minutes. Women using the product found Semicid non-irritating. Semicid is non-staining and has no unpleasant taste or odor.

When you consider all that—the safety, efficacy, and convenience of this new contraceptive—you can see why your patients will continue to use Semicid once they have tried it. Use only as directed.

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(Continued from Page 2)

PREVENTION OF NEURAL TUBE DEFECTS: The Role of Alpha-Fetoprotein—UCLA Forum in Medical Sciences—Number 20—Edited by Barbara F. Crandall, Division of Medical Genetics, Departments of Pediatrics and Psychiatry, University of California, Los Angeles, Center for the Health Sciences; and Mary A. B. Brazier, Brain Research Institute, University of California, Los Angeles. Academic Press, Inc., Publishers, 111 Fifth Avenue, New York City (10003), 1978. 264 pages, $16.50.

PROPRANOLOL AND SCHIZOPHRENIA—KROC FOUNDATION SERIES—Volume 10: Proceedings of a Conference Sponsored by the Kroc Foundation, December 1976, Santa Ynez Valley, California—Editors: Eugene Roberts, PhD, Director, Division of Neurosciences, City of Hope National Medical Center, Duarte, California; and Peter Amacher, PhD, Director, Conference Program, The Kroc Foundation, Santa Ynez, California. Alan R. Liss, Inc., 150 Fifth Ave., New York City (10011), 1978, 162 pages, $15.00 (available in Europe and the Middle East exclusively from European Book Service, Hogeweyselaan 119, WEESP, The Netherlands, price: 45.00 Dutch Guilders).

¿QUÉ PASÓ?—An English-Spanish Guide for Medical Personnel—Third Edition, revised and expanded—Martin P. Kantrowitz, MD, Assistant Professor, Department of Family, Community, and Emergency Medicine, University of New Mexico School of Medicine; Director, National Health Service Corps Cinical Support Program for rural New Mexico and southern Colorado; Antonio Mondragon, Coordinator of Chicano Student Services, University of New Mexico; and William Lord Coleman, junior at the University of New Mexico School of Medicine. The University of New Mexico Press, Journalism 220, Albuquerque, NM (87131), 1978. 69 pages, $2.95 (paperback).

REVIEW OF MEDICAL MICROBIOLOGY—13th Edition—Ernest Jawetz, PhD, MD, Professor of Microbiology and Medicine, Lecturer in Pediatrics, University of California, San Francisco, School of Medicine; Joseph L. Melnick, PhD, Distinguished Service Professor of Virology and Epidemiology, Baylor College of Medicine, Houston; and Edward A. Adelberg, PhD, Professor of Human Genetics, Yale University School of Medicine, New Haven. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1978. 550 pages, $12.00.

SIDE EFFECTS—Mel and Karen Silverstein. Doubleday & Company, Inc., 245 Park Ave., New York City (10017), 1978. 264 pages, $7.95.

SLEEP APNEA SYNDROMES—Kroc Foundation Series Volume 11—Editors: Christian Guilleminault, MD, Maitre de Recherche, Institut National de la Sante et Recherche Médicale, and Sleep Disorders Clinic and Research Center, Stanford University School of Medicine, Stanford, CA; and William C. Dement, MD, PhD, Professor of Psychiatry, Sleep Disorders Clinic and Research Center, Stanford University School of Medicine. Alan R. Liss, Inc., 150 Fifth Ave., New York City (10011), 1978. 390 pages, $34.00 (available in Europe, the UK and the Middle East exclusively from European Book Service, Hogeweyselaan 119, WEESP, The Netherlands, price: 102.00 Dutch Guilders).

A SURVEY OF HUMAN DISEASES—David T. Purtilo, MD, Department of Pathology, School of Medicine, University of Massachuestts. Addison-Wesley Publishing Company, Medical/Nursing Division, 2725 Sand Hill Road, Menlo Park, CA (94025), 1978. 453 pages, $15.95.

SYSTEMIC PATHOLOGY—Second Edition—Volume 3: ALIMENTARY SYSTEM—Edited by W. St C. Symmers, MD (Belfast), PhD (Birmingham), FRCP (London and Ireland), MRCP (Edinburgh), FRCPA, Professor of Histopathology in the University of London at Charing Cross Hospital Medical School; Honorary Consultant Pathologist, Charing Cross Hospital. Churchill Livingstone—Medical Division of Longman Inc., 19 West 44th St., New York City (10036), 1978. 465 pages, $45.00.

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PERCOCET®-5 Tablets (II)

Brief Summary of Prescribing Information

DESCRIPTION Each tablet of PERCOCET®-5 contains 5 mg oxycodone hydrochloride (WARNING: May be habit forming), 325 mg acetaminophen (APAP).

INDICATIONS For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS Hypersensitivity to oxycodone or acetaminophen.

WARNINGS Drug Dependence Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCOCET®-5, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, PERCOCET®-5 is subject to the Federal Controlled Substances Act.

Usage in ambulatory patients Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCOCET®-5 should be cautioned accordingly.

Interaction with other central nervous system depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCOCET®-5 may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in pregnancy Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, PERCOCET®-5 should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children PERCOCET®-5 should not be administered to children.

PRECAUTIONS Head injury and increased intracranial pressure The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions, which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions The administration of PERCOCET®-5 or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients PERCOCET®-5 should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

ADVERSE REACTIONS The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation, skin rash and pruritus.

DOSAGE AND ADMINISTRATION Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. PERCOCET®-5 is given orally. The usual adult dose is one tablet every 6 hours as needed for pain.

DRUG INTERACTIONS The CNS depressant effects of PERCOCET®-5 may be additive with that of other CNS depressants. See WARNINGS. 6085 BS

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EDO-25-1078

SOME PEOPLE CAN TOLERATE ANYTHING

PERCOCET-5

Each tablet contains 5 mg oxycodone HCl (WARNING: May be habit forming) and 325 mg acetaminophen (APAP) CII

FOR THOSE WHO CAN'T TOLERATE ASPIRIN

- □ indicated for moderate to moderately severe pain
- □ contains well-tolerated acetaminophen
- □ provides the effective analgesia of oxycodone
- □ scored tablet permits finer titration
- □ convenient, economical q6h dosage

Please see opposite page for brief summary of prescribing information.

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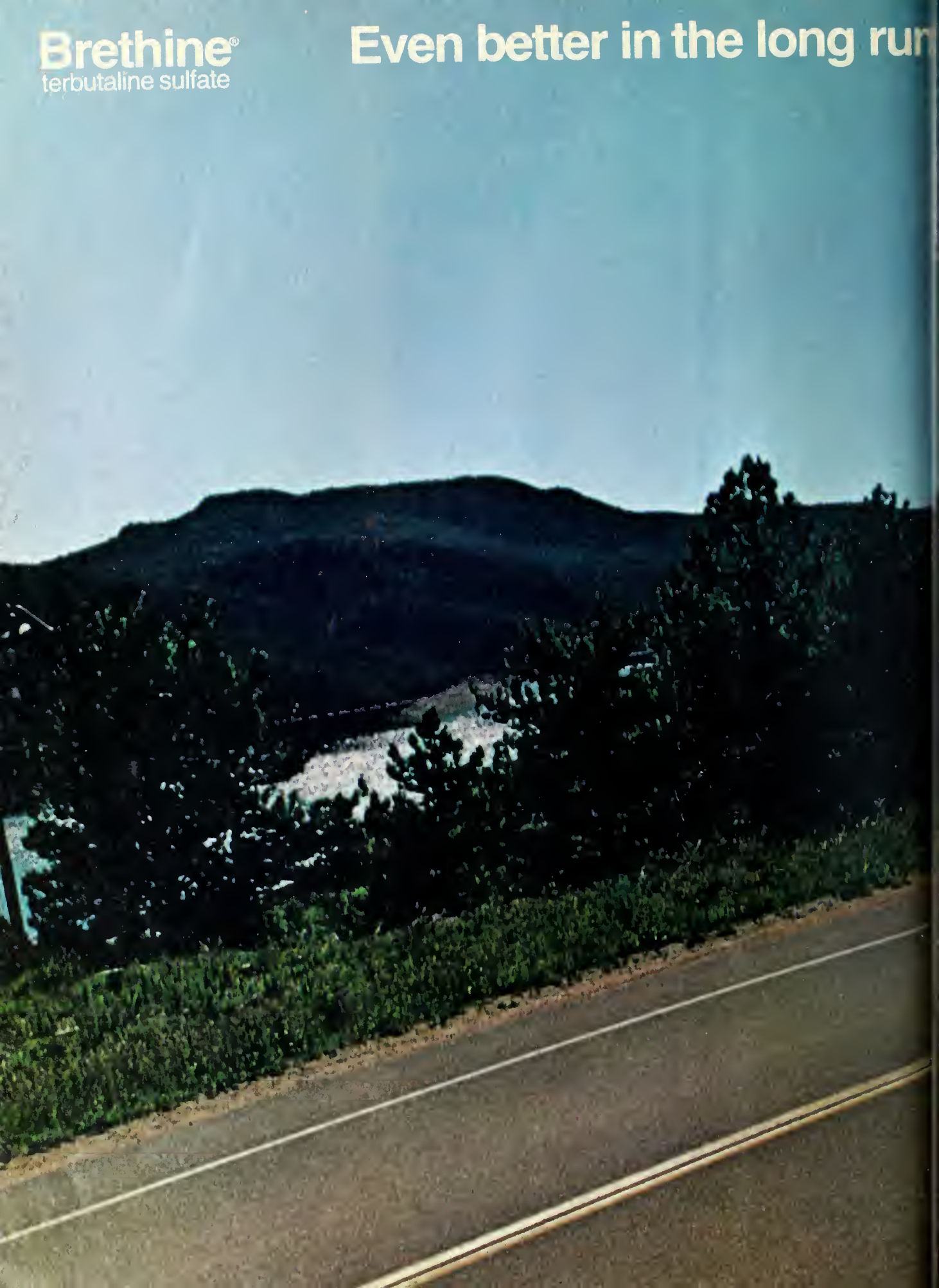
Brethine®
terbutaline sulfate

Even better in the long run



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ct, studies spanning 12 to 18 months[1-3] ate that Brethine not only retains the y to produce bronchodilation in asth- c and bronchitic patients, *but is also ciated with considerable improvement seline pulmonary function.*[2,3]

While therapeutic response remains highly effective, tremor and the modest cardiovascular effects associated with Brethine tend to diminish with continued use. To minimize tremor when initiating therapy, a starting dose of 2.5 mg is recommended. For details, please consult the prescribing information, a summary of which appears on the next page.

Brethine. In the long run, breathing is believing.

Brethine®
terbutaline sulfate

Now the most widely prescribed bronchodilator tablet on the [illegible]

In the long run, breathing is believing.

1. Formgren H: The therapeutic value of oral long-term treatment with terbutaline in asthma. Scand J Respir Dis *56*(6):321-328, 1975.
2. Larsson S et al: Lack of bronchial beta adrenoceptor resistance in asthmatics during long-term treatment with terbutaline. J Allergy Clin Immunol *59*(2):93-100, 1977.
3. Wilson AF et al: Cardiopulmonary effects of long-term bronchodilator administration. J Allergy Clin Immunol *58*(1):204-212, 1976.

Geigy

Brethine®, brand of terbutaline sulfate, Tablets 5 mg., Tablets 2.5 mg. *Before prescribing or administering, please consult complete product information, a summary of which follows:*

Tablets contain 5 mg (equivalent to 4.1 mg. of free base) or 2.5 mg. (equivalent to 2.05 mg. of free base) of Brethine, brand of terbutaline sulfate.

Indications: As a bronchodilator for bronchial asthma and for reversible bronchospasm which may occur in association with bronchitis and emphysema.

Contraindications: Known hypersensitivity to sympathomimetic amines.

Warnings: *Usage in Pregnancy:* The safety of the use of Brethine, brand of terbutaline sulfate, in human pregnancy has not been established. The use of the drug in pregnancy, lactation, or women of childbearing potential requires that the expected therapeutic benefit of the drug be weighed against its possible hazards to the mother or child.

Usage in Pediatrics: Brethine, brand of terbutaline sulfate, tablets are not presently recommended for children below the age of twelve years due to insufficient clinical data in this pediatric group.

Precautions: Brethine, brand of terbutaline sulfate, should be used with caution in patients with diabetes, hypertension, hyperthyroidism, and a history of seizures. As with other sympathomimetic bronchodilator agents, Brethine, brand of terbutaline sulfate, should be administered cautiously to cardiac patients, especially those with associated arrhythmias. Although the concomitant use of Brethine, brand of terbutaline sulfate, with other sympathomimetic agents is not recommended, the use of an aerosol bronchodilator of the adrenergic stimulant type for the relief of an acute bronchospasm is not precluded in patients receiving chronic oral Brethine, brand of terbutaline sulfate, therapy.

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Emergencies in Oncology

Current Management

DAVID C. STOLINSKY, MD, *Los Angeles*

Malignant neoplasms may cause life-threatening complications requiring prompt diagnosis and emergency therapy. Whether or not the underlying neoplasm is potentially curable, the physician can often provide worthwhile prolongation of life and dramatic symptomatic relief. Among the serious complications of neoplasia are superior vena cava obstruction, airway obstruction, pericardial tamponade, spinal cord compression, brain metastasis, meningeal involvement by cancer, hyperuricemia, hypercalcemia and hyperkalemia.

THE PRESENCE of a malignant neoplasm, especially one not potentially curable, sometimes evokes in a physician a feeling of nihilism and lack of urgency in diagnosis or therapy. This review is intended to focus attention on the major life-threatening complications of neoplasia that can be alleviated by prompt diagnosis and therapy. Space does not permit the inclusion of all the serious complications of neoplasia. Among those omitted are the complications due to increase or decrease of the cellular elements of the blood, hemorrhagic disorders, hyperviscosity, and such metabolic disturbances as hypernatremia and hyponatremia, hypoglycemia and lactic acidosis. By the same token, physicians must remain alert to the nononcologic complications that may occur in patients with cancer.[1]

Superior Vena Cava Obstruction

The superior vena cava is formed by the confluence of the innominate veins, which in turn arise from the confluence of the internal jugular and subclavian veins. The last major tributary of the superior vena cava is the azygos vein, which receives blood from the chest wall. If the superior vena cava is blocked above the entrance of the azygos, blood can bypass the obstruction through chest wall collaterals and reenter the superior vena cava via the azygos. If the obstruction is below the entrance of the azygos, blood must pass in a retrograde manner down the azygos and other chest wall veins to reach the drainage area of the inferior vena cava. Hence an obstruction below the level of the azygos is more poorly tolerated.[2]

A primary thoracic neoplasm is the cause in most patients. About 80 percent are due to lung cancer, more commonly on the right and more commonly in small cell carcinoma. About 15 percent of right upper lobe malignant lesions will result in superior vena cava obstruction.[2] Other neoplastic causes include lymphoma, thymoma and, rarely, metastatic tumors.[2,3] Although the syndrome was first described in 1757 in a patient with a luetic aortic aneurysm, benign causes are now very rare, making up less than 5 percent of cases.[2,3] Other benign causes are goiter, tuberculosis, sarcoid, mediastinitis, thrombosis,[2,3] and sternocostoclavicular hyperostosis.[4]

The clinical features are characterized by venous hypertension in the area normally drained

From the Medical Oncology Division, Department of Medicine, University of Southern California School of Medicine, Los Angeles.

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Reprint requests to: David Stolinsky, MD, Room 10-421, LAC-USC Medical Center, 1200 N. State St., Los Angeles, CA 90033.

by the superior vena cava.[2,3] Rapidly growing lesions are tolerated poorly; collaterals have insufficient time to develop.[5] One sees the rapid or insidious onset of facial and neck edema, accompanied by upper extremity edema (which may begin on one side). Distended neck veins are seen unless neck edema is severe enough to obscure them. Tortuous collateral veins are visible on the chest and upper abdomen in most patients,[2,3,5] Dyspnea may be caused by tracheobronchial obstruction. The increased intracranial pressure can result in headache, stupor, coma, seizures, cerebral hemorrhage, engorgement of the retinal veins and papilledema.[2,3] Esophageal obstruction may coexist.[2] Death may result from cerebral edema, airway obstruction or cardiac complications. At autopsy 70 percent of patients are found to have cardiac or pericardial metastases.[2]

Diagnosis should be easy, except in mild, early cases. Venous manometry adds little.[3] Infrared photographs[2] show the collateral veins nicely but are unnecessary. A venogram of the superior vena cava will localize the lesion and aid in evaluating collaterals.[2] However, a venogram is not necessary before starting therapy. Indeed, any venipunctures in the upper extremities should be avoided to prevent hemorrhage.[3] The risk of hemorrhage should make one reluctant to carry out a biopsy, whether scalene, bronchoscopic or mediastinal.[3] The risk of obtaining a tissue diagnosis, plus the overwhelming probability that the lesion is malignant, allow one to break the usual rule and begin therapy at once. Especially in a severe case, one should not delay therapy even one day to obtain unnecessary studies. Once therapy has reduced the venous pressure, a biopsy can be done more safely.

Irradiation is the mainstay of therapy.[2,3,6,7] Response occurs in greater than 80 percent of patients at doses of at least 4,000 rads.[2,6,7] If collaterals are well developed, minimal tumor shrinkage will bring clinical relief.[2] Giving 400 rads per day produces no more side effects than giving 200 rads per day.[2] The recurrence rate is only about 10 percent following a response.[2,3,6,7] Apparently even if the superior vena cava is again obstructed, collaterals have time to develop, so that the syndrome may not recur. Corticoids may be of transient benefit, even though radiation edema has not been shown to exist in this situation.[2] Nevertheless, many oncologists recommend their use before and during irradiation. Of course, in lymphoma corticoids can have a direct antitumor effect. Similarly, some experienced oncologists use emergency chemotherapy before starting irradiation. They point to the occasional patients whose conditions deteriorate rapidly during the first few days of irradiation. However, in randomized trials, nitrogen mustard (mechlorethamine) added nothing to irradiation.[2,6]

In most patients, chemotherapy is used after irradiation. In small cell lung cancer, and possibly in other very responsive tumors, it may be permissible to use combination chemotherapy without irradiation.[8] Further data should clarify this point. Chemotherapeutic agents should not be injected into high-pressure arm veins.[3] Ancillary measures may be of transient benefit.[3] Elevation of the head of the bed may partially alleviate brain edema. Diuretics may be of some use but are not free of side effects. Anticoagulant therapy and fibrinolytic therapy are of unproved value.[9] Surgical bypass of the obstruction may rarely be possible[10] but would play no role in most patients. About 10 percent of patients with lung cancer and 45 percent of those with lymphoma survive at least 30 months after the onset of the obstruction.

Airway Obstruction

Obstruction of the airway may result from fungating head and neck malignant lesions.[11,12] Extrinsic compression may be caused by neoplasms of the thyroid, lung or mediastinum—for example, thymoma. Uncommon causes include involvement of the Waldeyer ring by leukemia, lymphoma or heavy chain disease.[13-15] The clinical features are characterized by stridor, retraction and use of accessory muscles.[12] Superior vena cava obstruction may coexist.[3] Soft tissue x-ray films of the neck, an air bronchogram or tomography may show the obstruction.[11,12] Emergency tracheostomy or intubation may be necessary, if one can get below the level of obstruction.[11,12] Emergency surgical operation, irradiation or chemotherapy may be used, depending on the nature of the tumor. Corticoids may be tried, but they are of uncertain value except in lymphoid neoplasia.

Pericardial Tamponade

Neoplasms of the lung or breast, lymphomas, melanoma, leukemia and, rarely, other tumors may cause pericardial metastases, effusion and tamponade.[16,17] Irradiation to the mediastinum can cause pericarditis as an early or late compli-

cation,[18,19] and subsequent bleomycin therapy can bring it on as a "recall" phenomenon. Infection must always be ruled out. The clinical features include a reduced pulse pressure, paradoxical pulse, distended neck veins, the Kussmaul sign, quiet heart sounds and often a friction rub.[16,17] An enlarged, globular heart shadow may or may not be present on a chest radiograph. An electrocardiogram frequently shows low voltage, with or without ST abnormalities. Electrical alternans may occur. A clinically significant effusion is usually shown by echocardiography.

Prompt pericardiocentesis under electrocardiographic and perhaps echocardiographic control[21] can be life-saving. Some advise leaving a small catheter in place for several days. If the fluid contains malignant cells and the effusion recurs, intrapericardial injection of a chemotherapeutic agent may be tried[17] in responsive tumors. Fluorouracil has been used in doses of 500 to 1,000 mg or thiophosphoramide (THIOTEPA®) in doses of 15 to 30 mg. Data are insufficient to suggest which agent is preferable. It would seem wise to avoid extreme irritants such as nitrogen mustard (mechlorethamine) or quinacrine (atabrine) which might produce fibrosis and constriction, but there are no data on this point. Irradiation, either external or by intrapericardial injection of radioactive chromic phosphate, can be effective for neoplastic effusions.[17] Creation of a pericardial "window" may be carried out under local anesthesia[16] and should be considered if nonsurgical methods do not bring prompt relief. Pericardiectomy may be necessary for severe postirradiation changes in a patient with a good prognosis.

Therapy with corticoids can alleviate radiation-induced pericarditis.[18-20] On the other hand, in patients who have had mediastinal irradiation in the past, pericarditis may develop (for the first time) when administration of corticoids is stopped —such as in combination therapy of lymphomas.[20] For this reason, corticoids are being omitted from these patients' regimens.[20] Paradoxically, therefore, irradiation can cause pericarditis but is used to treat neoplastic pericardial involvement. Corticoids may precipitate radiation pericarditis by their withdrawal, but they are used to treat radiation pericarditis once it occurs.

Spinal Cord Compression

A metastatic tumor compressing the spinal cord is almost always extramedullary.[22-28] This complication may be seen with neoplasms of the lung, breast, prostate, kidney and thyroid, as well as in myelomas, lymphomas, leukemias, sarcomas and carcinomas of unknown primary.[22-28] Metastases may reach the cord via arteries, paravertebral veins, direct extension from an involved vertebra or through a foramen from a retroperitoneal tumor.[22]

The clinical features[22] include pain, either local or radicular, in 90 percent of patients. Paresthesias may be present. Early weakness may go undetected in a bedridden patient or one ill for other reasons. Later, gait disturbances, spastic paraparesis, extensor plantar responses and hyperreflexia supervene. A sensory level may not involve all sensory modalities initially. Sphincter loss is a late finding. Early diagnosis is of prime importance in avoiding paraplegia.[22-28] On the other hand, initial delay does not always mean hope is lost. Occasionally a patient may walk again although therapy was not begun until 27 days after the onset of weakness.[23] Hence one must strive for early diagnosis but should not abandon a patient in whom diagnosis was missed initially.

X-ray films or radionuclide bone scans show vertebral involvement in about 80 percent of patients.[22,24] Lumbar puncture should usually be done in conjunction with a myelogram;[22] the neurologic situation worsens after the tap in 8 percent of patients. Fluid should be collected for cytologic and chemical examination before contrast material is injected.[22] A myelogram shows the extent of the lesion and may show a second level of compression besides the obvious one. If the block is complete, cisternal or cervical puncture may be needed to delineate the lesion.

Laminectomy is usually the treatment of choice if the cord compression is due to vertebral collapse or to a radioresistant tumor.[22,24] Operative mortality is about 8 percent in these patients.[22,24] Up to half of all patients will be able to walk, but only 5 to 7 percent of paraplegic patients will be able to do so.[22] Surgical operation is followed by irradiation.[22] If the tumor is radiosensitive (for example, lymphomas, Ewing sarcoma, neuroblastoma or small cell lung cancer) *and* if there is no vertebral collapse, irradiation may be used without operation.[22,23,25,27] However, if the neurologic signs worsen, laminectomy will still be needed. Irradiation is also used in patients who would not tolerate surgical operation. There is no randomized trial of surgical treatment versus irradiation for metastatic tumors compressing the

cord. Chemotherapy may be used as an emergency measure before operation or irradiation, especially in responsive tumors.[22,27] Corticoids should be used as an emergency measure before definitive therapy; their use is supported by studies in animals.[22,23,25-28] The usual dosage of dexamethasone is 4 mg every six hours. Corticoids are often given during irradiation, but radiation edema has not been proved to exist in this setting.[22] It is obviously preferable to treat threatening lesions of the cervical, thoracic or lumbar vertebrae with irradiation and bracing than to await the appearance of a neurologic deficit. Back or neck pain is an important warning which should be investigated.

Brain Metastasis

The most frequent cause of brain metastasis is lung cancer; others include melanoma, breast, thyroid, stomach and testicular cancer, as well as trophoblastic cancer.[22,29] Lymphomas rarely occur in the brain as space-occupying lesions, except in immunosuppressed transplant patients.[28] The clinical picture[22] includes headache in 53 percent of patients. Seizures, either focal or generalized, occur in about 15 percent. Obtundation is apparent in 33 percent, but careful testing will show confusion in greater than 50 percent. Papilledema is seen initially in 25 percent of patients. Depending on the site of the lesion or lesions, one may find visual field cuts, hemiparesis, aphasia or reflex changes. It is of note that about 10 percent of "strokes" prove to be brain metastases.[22]

The computerized tomographic (CT) scan is probably the most useful diagnostic aid, especially when it is used with contrast injection.[22] The CT scan helps differentiate tumor, vascular accident, abcess, subdural hematoma and hydrocephalus, each of which may occur in a patient with cancer.[22] Radiographs of the skull may show calcification, pineal shift or bony lesions; the last can confuse the interpretation of radionuclide brain scans. Lumbar puncture should not be done unless it is necessary to rule out meningeal infection or metastases.[22] Brain stem herniation may occur, especially in the presence of papilledema or a posterior fossa lesion.

Radionuclide brain scans are useful but require careful interpretation. Gallium scans are often falsely normalized by corticoid therapy, while technetium scans are not.[30] Technetium scans are often positive in a vascular accident; gallium scans may also be. Either type of scan may be positive with skull or scalp lesions, either infectious or neoplastic; here the CT scan is most useful. Angiography is usually diagnostic but is less needed with the use of CT scans. An electroencephalogram is often abnormal but may contribute little clinically. Pneumoencephalography has little use since CT scans have become available. Echoencephalography may detect a midline shift or dilated ventricles, but it is less sensitive than a CT scan.

Therapy includes emergency use of corticoids; their effects may be transient but dramatic.[22,29] Dexamethasone, 4 mg every six hours, is usually effective, but much higher doses are occasionally needed. Hypertonic solutions have some role in the acute reduction of brain edema, but the effect is temporary. They should be used with caution in the presence of marginal cardiac or renal function.[29] Mannitol, 20 percent solution, as an intravenous infusion may be used in doses up to 100 grams in 24 hours. It equilibrates slowly, so there is less rebound effect than with urea.[29] Glycerol, 1 gram per kg of body weight by mouth every four to six hours, has much less activity. It is used for maintenance therapy by some authorities, not at all by others.[29] It can be given intravenously. Anticonvulsants are used for seizure control. They are not necessary prophylactically in a patient who has never had a seizure, unless the patient has had a craniotomy.[22] Irradiation of the whole brain at 2,000 to 4,000 rads, depending on the tumor type, is the treatment of choice. Corticoids are given before and during irradiation by most authorities, although the existence of radiation edema is not universally accepted.[22,29] Some cytotoxic agents enter the central nervous system in varying degrees (such as the nitrosoureas, hydroxyurea, procarbazine), but none substitutes for irradiation in the therapy of brain metastases. Craniotomy may very rarely be indicated for potentially curable disease, such as a patient in a complete remission of testicular cancer in whom an isolated brain metastatic lesion develops. In addition, in a patient cured of cancer a resectable brain tumor, such as a meningioma, may rarely develop. A statistical association of breast cancer and meningioma has been reported.

Meningeal Involvement by Cancer

Meningeal involvement is present at autopsy in 4 percent of all cancer patients[22] but is less common as an antemortem diagnosis. The more com-

mon causes include breast cancer, non-Hodgkin lymphoma (mainly histiocytic), and the acute leukemias, as well as cancer of the lung, stomach, pancreas, prostate, Hodgkin disease and melanoma.[22,28,31-35] For unknown reasons this complication is very rare in squamous cancers. In 8 percent of patients with meningeal involvement, this represents the first sign of a neoplasm.

The clinical features may include increased intracranial pressure from obstructive hydrocephalus, scattered focal signs such as cranial nerve and upper or lower extremity deficits, back pain, seizures and confusion.[22,28,31-35] Neck stiffness occurs in 16 percent to 25 percent of patients. The spinal fluid shows increased pressure in 64 percent, increased protein in 85 percent, and decreased glucose in 55 percent to 76 percent of patients. However, both protein and glucose values may be normal in 10 percent. A positive spinal fluid cytology is present by definition, but to show it one may need repeated taps and careful fluid examination after concentration by cytocentrifuge or nucleopore filter.[22,28] Bacterial and fungal infection must be ruled out. In leukemia cranial nerve palsies may occur in the absence of spinal fluid pleocytosis and require prompt irradiation.[22] Eosinophilia in the spinal fluid is a rare finding.[33]

Therapy may include irradiation, intrathecal chemotherapy, or both.[22] Irradiation to the vertebral column reduces marrow tolerance to future systemic chemotherapy, so that cranial irradiation may be combined with lumbar intrathecal chemotherapy, as is done in meningeal leukemia.[22] It should be noted that if spinal irradiation is used, it should extend to the inferior limit of the dural sac, not merely to the cord itself. The most commonly used intrathecal agent is methotrexate at a dose of 6.25 to 10 mg per sq meter given twice a week until the fluid is clear.[22] It is probably safer not to exceed 12 mg as a single weekly dose in adults. Alternate agents are cytarabine (Ara-C) at a dose of 30 mg per sq meter[22,28] or thiophosphoramide (THIOTEPA),[36] each given on a similar schedule. After the spinal fluid has cleared, monthly maintenance intrathecal chemotherapy is used by some authorities. If cranial irradiation is not used, intrathecal chemotherapy should be given via an Ommaya reservoir to assure adequate intracranial dosage.[22] Intrathecal agents should be diluted in preservative-free solutions such as normal saline or Elliot's B solution in an attempt to reduce the incidence of side effects.[28] About 58 percent of patients respond to therapy.[22,28] Response is probably better in cases of lymphoma, leukemia and breast cancer than in other neoplasms. Of those who respond, about half do not have clinical meningeal recurrence, but many still have meningeal tumor at autopsy. Either irradiation or intrathecal chemotherapy can produce neurologic side effects ranging from confusion and neck stiffness to severe encephalopathy or paraplegia.[22,28,36] The incidence of side effects is probably higher if both irradiation and intrathecal chemotherapy are given to the same region.[28] It may be difficult to distinguish these neurologic side effects from recurrent tumor or infection. Cultures, cytologic studies, and a CT scan are helpful.

For purposes of discussion, one may separate meningeal tumor involvement from cord compression. In practice this distinction may be difficult. One may see a discrete mass on myelography in a patient whose spinal fluid contains malignant cells.[22] In such a case, irradiation is probably preferable, although there is no definitive study on this point. Intrathecal agents may destroy free-floating cells or tiny tumor seedlings, but it is unreasonable to expect them to diffuse into a 1-cm mass in adequate concentration.

Hyperuricemia

Uric acid is the end product of purine metabolism. Its major source is cell breakdown and its major excretory pathway is renal. Hyperuricemia may occur as a result of increased production, decreased excretion or both.[37-40] Increased production occurs during rapid cellular proliferation, such as in hematologic neoplasia, or during sudden cell lysis as a result of chemotherapy or of irradiation. Decreased plasma uricolysis may also play a role.[41] Urates may precipitate in the renal tubules or ureters, causing ureteral colic, azotemia, oliguria and decreasing urate excretion, leading to a vicious cycle.

Prophylactic allopurinol should be given before chemotherapy or irradiation of sensitive tumors, especially with bulky disease or if the serum uric acid level is borderline or elevated before therapy.[37-40,42-44] Allopurinol inhibits xanthine oxidase, which converts hypoxanthine and xanthine to uric acid. Note that this enzyme also inactivates 6-mercaptopurine and azathioprine (Imuran®), so that when either of these agents is given with allopurinol, the dose of these agents should be cut to 25 percent to 33 percent of the

usual dose.[37] The dose of 6-thioguanine need not be cut. Allopurinol in doses of 300 to 600 mg per day will usually cause a fall in the serum uric acid level in about three days, so that its administration should be started two or three days before cytolytic therapy, if time permits. In an occasional patient higher doses of allopurinol will be required, but they act no faster. Secondary gout is rare, so prophylactic colchicine need not be added.[10] Uricosuric agents such as benemid are contraindicated; the object is to decrease renal urate excretion, not increase it. An investigational intravenously given solution of allopurinol has been used for patients unable to retain oral medication, but it acts no faster than the oral form.

Maintenance of urine output above 2 liters a day is important. Keeping the urine pH above 7.0 will greatly increase urate solubility. Sodium bicarbonate, 9 to 12 grams a day, may be required to do this. If large amounts of sodium cannot be used, such as in congestive failure, acetazolamide (Diamox®) in doses of 1 gm a day will usually alkalinize the urine temporarily until allopurinol becomes effective. Acetazolamide will aggravate metabolic (for example, lactic) acidosis and should be avoided in this circumstance. The urine should be observed for crystals in the presence of hyperuricemia. If oliguria occurs, therapy with mannitol may be tried. One may start with 12.5 grams of a 20 percent solution given intravenously over three minutes. If urine output increases to 40 ml per hour, a 20 percent solution may be infused at a rate sufficient to keep urine flow about 250 ml per hour until the serum uric acid falls to safe levels. The dose of mannitol is limited to 100 grams per 24 hours to avoid clinical features resembling water intoxication.[37,44] If these measures fail, peritoneal dialysis or hemodialysis[39,45] or flushing the ureters via retrograde catheters[46] may be considered. Clearly, prevention of this complication is far better than treatment.

Hypercalcemia

Hypercalcemia occurs in about 20 percent of patients with cancer. The most frequent mechanism is "direct" lysis of bone by osseous metastases. This mechanism is incompletely understood; prostaglandins may be involved.[47,48] In addition, hypercalcemia without detectable bony metastases may develop. Ectopic parathormone production has been reported in squamous carcinoma of the lung or head and neck, and also in renal cell, ovarian and other types of cancer. Only one or two cases of ectopic parathormone production by breast cancer have been reported; here a coexistent parathyroid adenoma is more likely.[49-55] Non-vitamin D sterols have been reported in breast cancer[56] but not confirmed.[57] Prostaglandins have been reported in renal cell cancer, and also in sarcomas, melanoma, and breast, ovary, and other types of cancer.[47,48] Osteoclast-activating factor has been reported in myeloma[58] and similar bone-resorbing factors in acute lymphocytic leukemia.[59] Estrogens, antiestrogens, androgens or progestins may cause hypercalcemia in breast cancer within one to three weeks after starting therapy.[60] This effect is not due to release of hypercalcemic factors by dying cancer cells, because it can occur in the absence of tumor shrinkage. The differential diagnosis of hypercalcemia includes vitamin D excess, the milk-alkali syndrome, adrenal insufficiency, hyperthyroidism, tuberculosis and sarcoid. Whatever the underlying disease, hypercalcemia may be brought on by dehydration or immobilization in bed; the former decreases excretion of calcium, the latter increases its removal from bone. Thiazides may also aggravate hypercalcemia.

The early clinical signs of hypercalcemia include nocturia, polyuria and polydipsia. Later findings include nausea and vomiting with dehydration, weakness, lethargy, constipation, hyporeflexia, oliguria and coma. Digitalis toxicity may be precipitated. Ectopic calcification is unusual, probably because of the short duration of malignant hypercalcemia.

General principles of therapy include treating the cancer when possible, encouraging ambulation, correcting dehydration, increasing calcium excretion, decreasing calcium removal from bone, reducing calcium intake and interruption of hormone therapy in cases of breast cancer.[50,61-65] For patients with serum calcium levels below 14 mg per dl, oral rehydration and ambulation may suffice. Normal saline solution should be given intravenously if oral intake is inadequate. Oral phosphate may be used if the serum phosphate level is not elevated.[64] If prostaglandin production is suspected, such as in renal cancer, one may try indomethacin or aspirin.[47,48] Prednisone, 60 to 80 mg per day, or other corticoids, may be effective within a few days to a week, making it more useful for chronic than for acute control of hypercalcemia.

For patients with dangerous elevations of

serum calcium (over 14 mg per dl) a more vigorous regimen is necessary.[63-65] Dehydration should be corrected within two hours, as cardiac and renal function allow. When urine flow reaches 100 ml per hour, furosemide, 40 to 200 mg, may be given intravenously every one to two hours. The saline infusion should be matched to the preceding hourly urine output; one may need 8 to 12 liters in the first 24 hours. The serum potassium level should be monitored every four hours and potassium, 20 to 40 mEq, added to each liter as necessary to prevent severe hypokalemia. Up to 50 mEq of magnesium per day may be needed, but it is less important because the effects of hypomagnesemia are counteracted by hypercalcemia. The careful monitoring this regimen requires is best done in an intensive care unit. Aggressive therapy is stopped when the serum calcium level falls below 14 mg per dl. One must keep in mind that about half of patients with hypercalcemia and cancer will have hypokalemia even before therapy.

Chemotherapeutic agents are especially useful when sodium intake must be limited. Their action does not depend on renal excretion and can occur in the presence of oliguria. Mithramycin at a dose of 25 μg per kg of body weight is given as a 30 to 60 minute infusion.[65-67] It is often effective in lowering serum calcium levels within 12 to 48 hours. A single dose usually has little toxicity except nausea. Repeated doses every three to seven days may be needed; here one may see thrombocytopenia, a bleeding tendency, leukopenia, liver enzyme elevations, renal damage, and occasionally hypocalcemia or hypokalemia.[65-67] Some authorities prefer mithramycin to forced diuresis even when oliguria is not present.

Actinomycin D and methotrexate also have calcium-lowering effects, but their toxic effects make them less useful. Intravenously given sodium phosphate is, in my opinion, rarely needed, although some authorities feel it has a role, especially in hypophosphatemic patients.[63-65] Complications include widespread calcifications, shock and renal failure. If intravenous phosphate is used, no more than 1 gram of elemental phosphorus should be given within eight hours.[64] Neither intravenously given nor orally given phosphate should be used if the serum phosphate level exceeds 4 mg per dl. Phosphate should also be avoided in the presence of significant renal insufficiency.[61] Chelating agents can cause a transient drop in serum calcium level but are nephrotoxic.[65] Calcitonin has been effective in doses of 3 to 6 MRC (Medical Research Council) units per kg of body weight per day and deserves further trial.[65,68] Hemodialysis may be effective in severe cases.

Hypocalcemia is an uncommon complication of cancer.[64,69,70] Calcitonin production by the tumor, sepsis, malabsorption, azotemia, hypomagnesemia, hyperphosphatemia, anticancer agents, hypoparathyroidism due to destruction of the glands by cancer or surgical operation, and increased calcium uptake by osteoblastic metastases may each play a role.[64,66,67,69-72]

Hyperkalemia and Hypokalemia

"True" hyperkalemia occasionally results from successful therapy of exquisitely sensitive tumors such as Burkitt lymphoma or acute lymphocytic leukemia.[71-73] Massive cell lysis releases life-threatening amounts of potassium, as well as phosphate and other electrolytes. Anticipation of this complication allows careful monitoring of serum electrolyte levels and renal function. Ion exchange resins and dialysis may be required. Hyperuricemia and hypocalcemia may coexist and should be watched for.

"False" hyperkalemia may occur with patients in whom platelet or leukocyte counts are elevated to a pronounced degree.[72,74] The cells lyse in the tube before the serum is separated for analysis, releasing intracellular potassium. A rapidly separated, heparinized specimen may show a normal (or at least less elevated) plasma potassium level. No therapy is required. Normal findings on an electrocardiogram help to allay anxiety.

Hypokalemia may occasionally be caused by a renal tubular defect, perhaps due to muramidase (lysozyme), in acute nonlymphocytic leukemia.[75] Other causes include severe diarrheal states caused by the Zollinger-Ellison syndrome, vasoactive-intestinal-polypeptide-producing islet cell tumors, colorectal villous adenoma, or intestinal lymphoma.[76] Hypokalemia, sometimes severe, may be seen in 52 percent of cancer patients who have hypercalcemia.[77] This fact must be kept in mind, especially when intensive diuretic therapy is begun.

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Endobronchial Metastases in Breast Carcinoma

ALLAN N. KRUTCHIK, MD; CHARLES K. TASHIMA, MD; AMAN U. BUZDAR, MD, *and* GEORGE R. BLUMENSCHEIN, MD, *Houston*

In a consecutive series of 1,628 patients with breast carcinoma, six cases of endobronchial metastases were diagnosed for an incidence of 0.4 percent. The median latent interval from the diagnosis of the primary carcinoma until the time of diagnosis of endobronchial metastases was 21 months. Endobronchial metastases can be the initial manifestation of recurrent cancer and can present with no abnormalities shown on x-ray films of the chest. Because of similar symptomatology, the diagnosis of endobronchial metastases may be confused with a central bronchogenic carcinoma but the histological appearance could differentiate the two entities. Local treatment with radiation therapy is usually inadequate and patients should also be treated with some form of systemic treatment such as chemotherapy. The median survival after the diagnosis of endobronchial metastases was 13 months.

ENDOBRONCHIAL METASTASES occur in only 2 percent of patients with solid tumors with renal and colorectal carcinoma being the most common extrathoracic tumors associated with endobronchial metastases.[1] However, recently breast carcinoma has been proposed as the most common tumor causing endobronchial metastasis.[2] During a two-year period, we have encountered six patients with breast carcinoma who had documented endobronchial metastases from breast carcinoma.

Methods and Results

From the period of July 1974 to December 1976 a review of 1,628 patients with breast carcinoma showed six cases (0.4 percent) of endobronchial metastases from breast carcinoma which were documented by bronchoscopy. Our chart review was limited only to cases in which there were grossly visible (macroscopic) endobronchial metastases. Cases in which bronchial washings (microscopic) alone were used as a basis for the diagnosis of metastatic breast carcinoma were eliminated from this study. The patients' clinical characteristics are summarized in Table 1. There are several salient and important features that are evident in this group of patients. First, in two of six patients, the x-ray studies of the chest at the time of diagnosis of endobronchial metastases showed no abnormalities. Second, in three of six, endobronchial metastases were the initial manifestation of recurrent carcinoma. Third, the median latent interval from the diagnosis of primary carcinoma until the time of diagnosis of

From the Medical Breast Service, Department of Medicine, The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, Houston.

Submitted February 2, 1978.

Reprint requests to: Allan N. Krutchik, MD, Department of Medicine, The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, 6723 Bertner Avenue, Houston, TX 77030.

TABLE 1.—*Patient Characteristics*

Patient	*Age of Patient at Time of EBM*	*Presenting Signs and Symptoms*	*Time Interval (months*)*	*Location of EBM*	*Chest X-ray*	*Sites of Disease Before Diagnosis of EBM*	*Survival After Diagnosis of EBM (months)*
1	54	Cough, hemoptysis, dyspnea	20	LUL bronchus	Atelectasis, pleural effusion	Soft tissue	13
2	36	Cough	8	RUL bronchus	Atelectasis	None	36
3	54	Dyspnea, hoarseness	84	RUL bronchus	Normal	Soft Tissue	8†
4	72	Cough	8	RLL bronchus	Normal	None	24
5	33	Cough, wheezing	21	RLL bronchus	Pleural effusion	None	14
6	60	Hemoptysis, hoarseness	68	LUL bronchus	Loss of lung volume	Soft tissue	11†

EBM = endobronchial metastases LUL = left upper lobe RLL = right lower lobe RUL = right upper lobe

*Time interval between diagnosis of primary breast carcinoma and the diagnosis of endobronchial metastases.
†Alive at time of this review (November, 1977)

endobronchial metastases was 21 months (range 8 to 84 months). Fourth, localized radiation therapy was attempted in three of six patients with relief of symptoms in one patient. Fifth, the median survival after the diagnosis of endobronchial metastases was 13 months (range 8 to 36 months).

Reports of Cases

CASE 1. In a 53-year-old woman a right radical mastectomy was carried out; 11 of 13 lymph nodes contained metastatic breast carcinoma. The patient received postoperative radiation therapy to the peripheral lymphatics. In September 1974, she was again treated with radiation therapy for a right supraclavicular metastasis and received concomitant hormonal therapy. In February 1975 dyspnea and a productive cough developed with occasional hemoptysis; a small pleural effusion on the left was seen on an x-ray film of the chest. Subsequently, complete atelectasis of the left lung developed. Bronchoscopy showed an endobronchial mass occluding the left upper main stem bronchus and biopsy of this lesion showed metastatic breast carcinoma. The patient was treated with combination chemotherapy and within ten days the left lung had completely reexpanded and the pleural effusion disappeared. The pleural effusion reoccurred in eight months with a rightward shift of the mediastinum. Bronchoscopy showed an endobronchial mass in the right main stem bronchus at that time, which was treated with localized radiation therapy without improvement. Four months after bronchoscopy, meningeal carcinomatosis developed and the patient died.

CASE 2. A 36-year-old woman had a right radical mastectomy for breast carcinoma in 1969. She was well until February 1974, when a nonproductive cough and dyspnea developed. An x-ray study of the chest showed right hilar adenopathy and enlargement of the azygous vein. The patient was given a trial of antibiotics without relief. Subsequently, rhonchi and chest pain over the right hemithorax posteriorly developed. Eight months later a bronchoscopy was carried out and showed stenosis of the right upper lobe bronchus with an endobronchial metastasis present which on biopsy was found to be metastatic breast carcinoma. There was no evidence on bronchoscopy that the endobronchial metastasis represented an extrabronchial tumor arising from the right hilum that was eroding into the bronchus. Shortly after this, liver and bone metastases developed and a bilateral oophorectomy was carried out; a partial remission was obtained. Subsequently the patient was treated with adrenalectomy and combination chemotherapy. The patient died of pulmonary metastases 36 months after the diagnosis of endobronchial metastases was made.

CASE 3. In a 54-year-old woman a left mastectomy was carried out. Metastatic breast carcinoma was found in one out of two axillary lymph nodes and postoperative radiation therapy was administered. Five years later a skin recurrence developed and bilateral oophorectomy was done, followed by sequential androgen therapy. Shortly after the skin metastases, metastases to the right breast developed and a simple mastectomy was done. The patient later was treated with combination chemotherapy for soft tissue metasases and a partial remission was obtained. Seven years after the diagnosis of primary breast carcinoma, hoarseness and dyspnea developed. A bronchoscopy showed an endobronchial metastasis in the right main stem bronchus. Indirect laryngoscopy showed left vocal cord paralysis but no tumor was found. The patient was then treated

with combination chemoimmunotherapy: 5-fluorouracil, doxorubicin hydrochloride (Adriamycin®), cyclophosphamide and levamisole with stabilization of disease and is alive at this time.

CASE 4. A left radical mastectomy was carried out in a 72-year-old woman. Metastatic breast carcinoma was found in 24 of 46 nodes. Postoperatively radioactive gold seeds were implanted in the chest wall. Eight months later a persistent nonproductive cough developed; an x-ray film of the chest done at that time showed no abnormalities. Bronchoscopy showed an endobronchial metastasis in the right lower lobe bronchus. The patient was then treated with radiation therapy to the involved lung without improvement. Subsequently, she was treated with estrogens followed by combination chemotherapy. There was stabilization of disease until two years later when brain metastases developed along with progressive pulmonary metastases, both unresponsive to further chemotherapy. The patient died two years after the diagnosis of endobronchial metastases was made.

CASE 5. In a 33-year-old woman a right modified radical mastectomy was done in March 1974. There were no axillary node metastases. Postoperative radiation therapy was given because of the location of the carcinoma (medial lesion). In May 1974 a prophylatic left simple mastectomy was carried out. In October 1975 a cough, wheezing, a low grade temperature and a right pleural effusion developed. She was treated for pneumonia but the symptoms persisted. Bronchoscopy then was carried out and an endobronchial tumor was found occluding the right lower lobe bronchus; a biopsy of this tumor showed metastatic breast carcinoma. The patient was treated with combination chemotherapy consisting of 5-fluorouracil, doxorubicin hydrochloride (Adriamycin), cyclophosphamide and then methotrexate was substituted when the dose of doxorubicin hydrochloride reached 450 mg per sq meter. In December 1975 a bilateral oophorectomy was done because of recurrent pulmonary metastases. After there was an objective response to oophorectomy in regard to lung metastases, brain metastases developed. This condition was treated with various therapies including radiation therapy. In January 1977 respiratory distress developed and bronchoscopy was done; endobronchial metastases were seen in the area of the carina. The patient then received radiation to the left lung with a good response. However, after this, progressive pumonary disease developed and the patient died 16 months after the diagnosis of endobronchial metastasis was made.

CASE 6. A left radical mastectomy was done in a 60-year-old woman in April 1971 for Paget disease of the breast; axillary lymph node metastases were treated with postoperative radiation therapy. In February 1976 hoarseness developed, followed by supraclavicular metastases. Radiation therapy to the left supraclavicular area and to a mediastinal mass was administered. In October 1976 dyspnea and hemoptysis developed. Bronchoscopy was carried out and showed endobronchial obstruction of the lingular portion of the left lung with a tumor compatible with breast carcinoma. Treatment was carried out with combination chemoimmunotherapy consisting of 5-fluorouracil, doxorubicin hydrochloride (Adriamycin), cyclophosphamide and Corynebacterium parvum. The patient noted subjective improvement after chemotherapy was initiated and continued to do well until August 1977, when hemoptysis reappeared along with dyspnea. A bronchoscopy was done which showed an endobronchial metastasis obstructing the left upper lobe bronchus. This relapse indicated drug resistance and the patient was treated with a four-day infusion of amphotericin B followed by the same chemotherapy that the patient had received previously with no response. She is currently being treated with vincristine and methotrexate; the disease is stable.

Discussion

The symptoms and signs of endobronchial metastases from an extrathoracic tumor may be indistinguishable from central bronchogenic carcinoma; however, histological appearance should readily differentiate the two entities. The presence of carcinoma *in situ* in adjacent bronchial epithelium clearly indicates primary bronchogenic carcinoma.[1] Endobronchial metastasis can occur before the clinical appearance of the primary tumor and therefore it can mimic bronchogenic carcinoma.

In the absence of common roentgenographic signs of bronchial obstruction such as atelectasis,[1] there may be a low index of suspicion of endobronchial metastasis. This was the case in two of six patients who presented with normal findings on x-ray studies of the chest at the time of diagnosis of endobronchial metastases. In addition two patients presented with pleural effusions. Although we have no definitive evidence that the

pleural effusions that occurred were caused by endobronchial metastasis, there is evidence in the literature that pleural effusions can be produced by endobronchial metastasis.[3] In three of the six patients endobronchial metastases developed as the first site of relapsing disease from breast carcinoma; in one of these three patients x-ray films of the chest showed no abnormalities, with the only symptom being a cough. As recently reported, endotracheal metastases from breast carcinoma may present with symptoms of cough and hemoptysis and this could cause difficulty in diagnosing endobronchial metastases. However, tracheal tumors usually do not obstruct a single bronchus and one should not expect to see atelectasis of a lung. With normal findings on an x-ray film of the chest, tomography of the trachea should be obtained to resolve the dilemma.[4]

The mean survival of our group of patients after the diagnosis of endobronchial metastases was 13 months. Two patients, however, survived 24 and 36 months, respectively; this is considerably less than another small, recently reported group of patients with breast carcinoma whose mean survival was 29 months.[2]

Because of the small number of patients both in our series and in the literature, it is difficult to make specific recommendations for the treatment of endobronchial metastases. Radiation therapy in our series was unsuccessful even in the one patient who initially benefitted because of the subsequent development of distant metastases. Therefore, while radiation therapy is effective for short-term control of local disease, most patients relapse when this is the only modality of treatment used.[2] In view of the excellent response achieved in the patient in case 1 within a short time after the institution of combination chemotherapy and also because of another reported case in which the patient received excellent palliation with hormonal therapy (fluoxy-mesterone) followed by chemotherapy,[2] we recommend that systemic therapy should be employed in these patients. It has been shown that following an isolated recurrence in breast cancer, systemic disease is already present in a high percentage of patients or will soon develop. Some 3 to 21 percent of patients have been reported to survive five years following regional therapy—surgical or radiation therapy, or both—after the first evidence of recurrence.[5,6] A combination of 5-fluorouracil, doxorubicin hydrochloride (Adriamycin) and cyclophosphamide has significantly prolonged the disease-free interval following regional therapy of isolated recurrence.[7]

Endobronchial involvement is not necessarily associated with a poor prognosis as noted by mean survival in excess of 12 months, with a few patients surviving beyond two years. Therefore, all of these patients should be treated with systemic therapy in addition to the local therapy—radiation or surgical therapy, or both—that is administered for relief of symptomatic obstruction.

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Urinary Tract Infection/Vaginitis Protocol

Use in a Walk-in Clinic

JOHN E. CONTE, JR., MD, *San Francisco*

A process, outcome and salary-cost analysis was made of the use of a urinary tract infection/vaginitis protocol. Three nurse practitioners, in a university-based, walk-in clinic, cared for 128 women presenting with complaints of dysuria or vaginal discharge, or both. There were no significant differences among the nurse practitioners in data collection, diagnostic accuracy or patient outcome. The diagnoses were correct in 92 percent, incorrect in 6 percent and indeterminate in 2 percent of the patients. Incorrect diagnoses were due to presumption of urinary tract infection in patients with the urethral syndrome or vaginitis. Of the patients, 78 percent were actually sent home without seeing a physician. Concordance with the nurse practitioners' physical examination was 100 percent in those patients examined by a physician. In 82 percent of the patients there was alleviation of symptoms. Patient satisfaction with this method of care was extraordinary, with 98 percent of the patients giving favorable reports. True physician extension was achieved with a reduction in physician time per patient from 20 minutes to 6 minutes. In contrast to previously reported data, only a modest reduction in salary cost savings (10 percent) could be shown. The author concludes that nurse practitioners working in an acute care clinic or emergency department can see the patients defined in the study and provide high-quality care at a reasonable cost.

SINCE 1973 the University of California in San Francisco has provided drop-in medical care for adults in the screening and acute care clinic. As the community has become aware of this service, utilization of the clinic has progressively increased. Many of the patients are women with complaints suggestive of vaginal or urinary tract infections.

Reports from a number of centers indicate that nurse practitioners using protocols can effectively treat outpatients with a variety of problems. These problems include low back pain,[1] streptococcal pharyngitis,[2] upper respiratory tract complaints,[3,4] dysuria and vaginal discharge.[4,5] In addition nurse practitioners can provide other forms of primary care.[6,7]

Greenfield and co-workers, in a controlled trial, showed that a nurse practitioner using a dysuria protocol and a vaginitis protocol delivered effective care to women in a university health service. They concluded that the care was safe and would have resulted in physician time-saving if the referral recommendation in the protocols had been carried out. However, in that trial all the patients were examined by physicians.

The study reported here was designed to evalu-

From the Department of Medicine, Division of Emergency Medicine and Infectious Disease Unit, University of California, San Francisco.

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Reprint requests to: John E. Conte, Jr., MD, Emergency Department, Room 131, Moffitt Hospital, University of California, San Francisco, San Francisco, CA 94143.

ate the use of the dysuria and vaginitis protocols in an open, university-based walk-in clinic. The following questions were asked: Does the use of the protocols in this setting result in verifiable, high-quality patient care? Is the cost of the care rendered in this manner reasonable?

An extensive process, outcome and cost analysis of the care of 128 protocol-managed patients forms the basis for this report.

Materials and Methods

The screening and acute care clinic has an average monthly census of 1,600 patients and is staffed by salaried physicians, nurses, medical students and clerical personnel. It is open to the public 12 hours a day, six days a week. Patients presenting with complaints suggestive of serious illness are triaged to the emergency department and therefore are not seen in the clinic.

Three nurse practitioners used either or both of two protocols; one for the evaluation of dysuria and the second for vaginal discharge. Both were adapted from protocols originally described by Greenfield and associates.[5] The nurses are directed to the use of a specific protocol by a patient's presenting complaint; for example, "painful or frequent urination" requires use of the dysuria protocol and "vaginal discharge" requires use of the vaginitis protocol. If both complaints were present, both protocols were used. The protocol directs the nurse practitioner to elicit and record the patient's subjective complaints, take a medical history, carry out a limited physical examination and initiate tests. The protocol then directs the user to an assessment of the patient's condition and diagnosis. Depending upon the diagnosis and the findings, the nurse either initiates therapy and follow-up after a brief discussion with a physician or requests a physician consultation. Follow-up is undertaken by telephone contact within a week of the initial visit or analysis of subsequent clinic visits.

Three levels of physician consultation for the nurse practitioner are defined and required by the protocols: (1) brief verbal consultation with a physician after the evaluation was completed and the therapeutic plan formulated; (2) more extensive verbal consultation as specified in certain sections of the protocol when unusual or complicated history was present, and (3) interview and examination of the patient by the physician when abnormal physical findings were present.

After one of the above interactions, the physician was asked to complete a form describing his degree of involvement and overall evaluation of the care of the patient. (Tables 7 and 8.)

Patient satisfaction was evaluated by asking each patient to complete a short questionnaire which included the following: (1) Were you interviewed promptly by the clerk on duty? (2) Was the clerk courteous and efficient? (3) Did you see the nurse practitioner promptly? (4) Were you satisfied with the care you received today from the nurse practitioner? (5) Were you satisfied with your overall experience at the screening and acute care clinic?

Time spent by the nurse practitioners and physicians involved with the protocol patients was estimated by each of the clinic staff. These estimates were obtained intermittently throughout the study and at the completion of the study. Final time estimates for each degree of physician contact and for nurse practitioner time were calculated as an average of estimated times for each category. Cost savings were calculated using an average salary rate of $8 per hour for nurse practitioners and $18 per hour for staff physicians.

Each medical record was audited by the author using a prearranged set of criteria, summarized in Tables 2 and 3. Expected compliance for each of the entries was set at 100 percent—that is, the audited item was to be present in every record.

At biweekly meetings with each of the nurse practitioners the results of the current audits, follow-up contact and patients' medical records were discussed. Progress of the study was made available to clinic personnel.

At the end of the study, data from the audits were transferred to punch cards and entered into a computer for statistical analysis.

Laboratory tests in the clinic were done by the nurses as directed by the protocols and as described by Greenfield.[1] A diagnosis of urethral syndrome was made if, in a patient with dysuria, the urine culture was negative and vaginitis was not present.

Results

In all, 128 patients were included in the study. The dysuria protocol alone was completed in 14 patients, the vaginitis protocol alone in 96 patients and both protocols in 18 patients.

The youngest patient was 17 and the oldest 66 years old, with an average age of 27.

Follow-up was attempted for each patient seen in the clinic: 61 patients (48 percent) were con-

tacted by telephone and 42 patients (33 percent) were seen again in the clinic; follow-up was not possible for 25 (19 percent) patients. However, all patients were advised to return to the clinic if symptoms persisted. Diagnoses are summarized in Table 1.

TABLE 1.—*Summary of Diagnoses*

Diagnosis	*Number*
Nonspecific vaginitis	41
Candida vaginitis	39
Trichomonas vaginitis	14
Urethral syndrome	9
Urinary tract infection	6
Herpes genitalis	4
Nonspecific vulvitis	4
Pelvic inflammatory disease*	3
Foreign body in vagina	3
Nonspecific cervicitis	2
Gonococcal cervicitis	2
Normal examination findings	2
Endometriosis	1
Chlamydial cervicitis	1
Cystocele	1
Phagdenic ulcer	1
Venereal warts	1
	134†

*Cultures for Neisseria gonorrhea in these three patients were negative.

†Total is more than the number of patients because several patients had more than one diagnosis.

Data Base Acquisition

Appropriate statements regarding sexual activity and the possibility of venereal disease exposure were recorded in 100 percent of the 114 patients in whom the vaginitis protocol was used (Table 2). With the exception of Venereal Disease Research Laboratory tests, all of the data were present in greater than 90 percent of the records. Data collection using the dysuria protocol (Table 3) was less complete. For example, under History, the statement regarding genitourinary or gynecological procedures was recorded in 81.3 percent of patients; a statement regarding general appearance was recorded in 87.5 percent, and presence or absence of flank tenderness was recorded in 81.3 percent of patients. All other data were recorded in greater than 90 percent of patients.

Diagnostic accuracy by protocol is summarized in Table 4.

The physicians involved were satisfied with the

TABLE 2.—*Data Base Acquisition by Nurse Practitioner Using Vaginitis Protocol**

	Number of Patients	*Observed Percent Compliance*	*Expected Percent Compliance*
Statement regarding presence or absence appropriately entered in record			
Subjective			
A. Vaginal discharge	113	99.1	100
B. Abdominal pain, back pain	110	96.5	100
C. Nausea, vomiting, fever, chills	112	98.2	100
D. Genitourinary or rectal symptoms	113	99.1	100
History			
A. Previous vaginitis; pelvic inflammatory disease	112	98.2	100
B. Contraceptive use, menstrual history, pregnancy history	114	100	100
C. Drug allergy	108	94.7	100
D. Sexual activity; veneral disease exposure	114	100	100
E. Diabetes	109	95.6	100
F. Current medication use	113	99.1	100
Statement regarding objective findings appropriately entered in record			
Objective			
A. General appearance	103	90.4	100
B. Blood pressure and pulse	108	94.7	100
C. Pelvic examination	113	99.1	100
Laboratory tests appropriately done or ordered, or both			
Laboratory			
A. Microscopic	113	99.1	100
B. Gonoccal cultures indicated	113	99.1	100
C. Veneral disease research laboratory test	99	86.8	100

*The vaginitis protocol was used in a total of 114 patients. The dysuria protocol was also completed in 18 of these 114 patients.

overall care rendered by the nurse practitioners in 123 of the 124 patients for whom evaluation forms were submitted (Table 5). In one instance, the physician felt that a chlamydial culture should have been obtained in a patient with cervicitis. Chlamydial cultures, however, were not a routine part of the protocol.

There was agreement with the nurse practitioners' findings in all 28 patients where the protocol called for interview and examination by a physician.

Antibiotic use, as directed by the dysuria protocol, is summarized in Table 6. Quantitative urine culture was done in all patients. In six of the 32 patients with symptoms suggesting urinary tract infection, cultures were positive. Of the 32, a total of 12 (38 percent) had vaginitis with negative urine cultures; 9 (28 percent) had the urethral syndrome. In five patients (16 percent) a microbiologic cause for the urinary tract symptoms could not be proven. The symptoms in these patients were attributed to psychosomatic factors or endometriosis, or were felt to be indeterminate.

Antibiotic therapy was appropriately instituted in all six patients with culture-proven urinary tract infections. Of the remaining 26 patients, antibiotic therapy was instituted appropriately according to the protocol criteria in nine and inappropriately in one. In these patients, the antibiotic administration was stopped when the urine culture was known to be negative. In one patient the urine culture was lost; the antibiotic therapy was continued and the diagnosis judged to be indeterminate.

None of the patients for whom the vaginitis protocol only was completed received an orally

TABLE 4.—*Accuracy of Diagnosis*

	Number of Patients			
	Number in each Category	*Correct Diagnosis*	*Incorrect Diagnosis*	*Indeterminate Diagnosis*
Vaginitis protocol* alone	96	95	0	1
Dysuria protocol* alone	14	7	6	1
Both protocols	18	16	2	..
Total	128	118	8	2

*The difference in diagnostic accuracy between the protocols did not achieve statistical significance: p=0.11; Fisher's exact test.

TABLE 3.—*Data Base Acquisition by Nurse Practitioner Using Dysuria Protocol**

	Number of Patients	*Observed Percent Compliance*	*Expected Percent Compliance*
Statement regarding presence or absence appropriately entered in record			
Subjective			
A. Dysuria, frequency, urgency, hematuria	32	100	100
B. Nausea, vomiting, chills, fever	31	96.9	100
C. Suprapubic pain	31	96.9	100
D. Back pain	31	96.9	100
E. Vaginal discharge	32	100	100
History			
A. Previous urinary tract infection or kidney disease	31	96.9	100
B. Genitourinary or gynecological surgery or procedures	26	81.3	100
C. Relationship to sexual activity	30	93.8	100
D. Current medications	31	96.9	100
E. Drug allergy	31	96.9	100
Statement regarding objective findings appropriately entered in record			
Objective			
A. General appearance	28	87.5	100
B. Flank tenderness	26	81.3	100
C. Suprapubic tenderness	30	93.8	100
Laboratory tests appropriately done or ordered, or both			
Laboratory			
A. Microscopic	32	100	100
B. Protein, glucose	32	100	100
C. Urine culture	32	100	100

*The dysuria protocol was used in a total of 32 patients. The vaginitis protocol was also completed in 18 of these 32 patients.

given antibiotic in the clinic. Three patients with the diagnosis of pelvic inflammatory disease were referred to the emergency department where antibiotic therapy was initiated.

Outcome was evaluated using degree of patient satisfaction, alleviation of symptoms and cure of culture-proven urinary tract infection as criteria (Table 7).

Patient satisfaction forms were completed by all of the patients and only two described annoyance associated with a long wait at the clinic. Neither complained about the skill level of the nurse practitioners or quality of care, or about not being examined by a physician.

Follow-up was not available for 24 of the 128 patients; they are considered indeterminate. Of 104 for whom follow-up was available, 85 (82 percent) had alleviation of symptoms. The most common diagnosis in the 19 patients who did not have alleviation of symptoms was vaginitis. In 11 of these the cause was "nonspecific," in 3 trichomonas and in 2 candida. One patient had chronic pelvic inflammatory disease. In two patients who did not have alleviation of symptoms the diagnoses were "of unknown etiology" (one patient) and the urethral syndrome (one patient).

Five of the six patients with culture-proven urinary tract infections were cured as measured by a negative follow-up culture. In one patient a urine culture was omitted on the follow-up visit but the patient was asymptomatic and there were no cells or bacteria on microscopic examination of a urine specimen. This patient was regarded cured. Table 8 summarizes the three levels of physician involvement and the time spent per patient for each category.

Calculated average time spent and salary costs per patient visit are summarized in Table 9. The physician time spent was six minutes and the physician salary cost per protocol patient was $1.80. The nurse practitioner time spent was 26.7 minutes and cost per protocol patient was $3.56. Therefore, the total salary cost (physician and nurse) per protocol patient was $5.36. Without the use of protocols, physicians in the clinic estimated that patients with complaints of dysuria and vaginal discharge are seen at the rate of three per hour (20 minutes per patient). The average physician cost per patient without protocol care, therefore, amounts to $6.00.

Discussion

In 1974 Greenfield and his associates published the urinary tract infection/vaginitis protocols used in this study.[5] In all, 140 patients in a university health service were cared for by one nurse practitioner in that study. The authors concluded that the resultant care was of high quality, safe and would have saved time for physicians if the recommendations of the protocol had been implemented.

The study reported here was done to examine critically the quality of care and salary cost aspects of the use of the protocols in an open walk-in clinic. As much as possible, the usual clinic routines were not interfered with. The audit was conducted using the medical records generated by the three nurse practitioners. It is important to emphasize that the physician interaction recommendations of the protocol were actually carried out. Patients were not asked routinely to

TABLE 6.—*Diagnosis and Antibiotic Use in Patients for Whom the Dysuria Protocol Was Completed*

Diagnosis	*Patients*	*Percent*	*Number Receiving Oral Antibiotics*
Urinary tract infection alone	5	16	5
Urinary tract infection and vaginitis	1	3	1
Vaginitis alone	12	38	2
Urethral syndrome	9	28	7*
Other	5	16	1
Total	32	100	16

*One patient in this group was inappropriately given an antibiotic; microscopic criteria for therapy were not present but treatment was begun because of the patient's history of previous urinary tract infections.

TABLE 5.—*Physician Satisfaction with Nurse Practitioner Care and Concordance with Physical Examination*

	Yes	*No*	*Indeterminate*	*Total*
Physician satisfaction with care given by nurse practitioners (all patients)	123	1	4	128
Physician agreed with nurse practitioner in those patients requiring examination by the physician (28 patients)	28	0	0	28

return to the clinic for reevaluation (except those with urinary tract infection) because this is usually unnecessary for patients with these minor acute illnesses.

In spite of the attempt to maintain a business-as-usual routine in the clinic, a positive bias has almost certainly been introduced into these results. All of the clinic personnel knew that the care of protocol patients was being audited. Results of the audit were made available to the staff. In addition, the motivation and enthusiasm of the nurse practitioners was very high because this was a new patient care activity and because they felt personally challenged by the audit.

Despite these limitations, we feel that a number of conclusions are justified.

Data base acquisition for the protocol patients was excellent. Comparative figures for these protocols are not in the literature. However, the compliance rates for all categories of information were high. There were no significant differences between the nurse practitioners or between protocols in data collection.

The high degree of diagnostic accuracy previously reported for nurse practitioners using these protocols is confirmed in this study. There were no significant differences among the three nurse practitioners or between the protocols. In 96 patients for whom the vaginitis protocol only was completed the diagnosis was correct in 95 and indeterminate in one. In 14 patients for whom the dysuria protocol only was completed, the diagnosis was correct in seven, incorrect in six and indeterminate in one. Of the six patients in whom the diagnosis was incorrect, the nurse practitioner had made an appropriate assessment as specified by the protocol. In these cases, presumptive diagnosis of urinary tract infection was made on the basis of microscopic findings in the urine. However, all six patients had negative urine cultures and were judged to have the urethral syndrome. Of the 18 patients for whom both pro-

TABLE 9.—*Time Spent and Salary Costs per Patient Visit*

	Average Time Per Patient Visit (minutes)	*Average Salary Cost Per Patient Visit*
Physicians with protocol-managed patients	6	$1.80
Nurse practitioners with protocol-managed patients	26.7	$3.56
Total		$5.36
Physicians without nurse practitioner protocol care*	20	$6.00

*Based on estimates by clinic physicians of three patients per hour without nurse practitioner protocol care and an hourly rate of $18 for physicians.

TABLE 7.—*Patient Outcome*

	Determinate Diagnoses						*Indeterminate Diagnoses*
	Yes	*Percent*	*No*	*Percent*	*Total*	*Percent*	*Number*
Patient satisfied with care	126	98	2	2	128	100	0
Alleviation of symptoms	85	82	19	18	104	100	24
Cure of culture-proven urinary tract infection	6	100	0	0	6	100	0

TABLE 8.—*Physician Involvement With Patient Care and Time Estimates*

	Patients		*Physician Time per Patient in this Category (minutes)*	*NP Time per Patient in this Category (minutes)*
	Number	*Percent*		
Brief discussion with nurse practitioner, sign chart and prescription, no examination	78	61.5	3.5	23.5
More extensive verbal consultation with nurse practitioner, sign chart and prescription, no examination	21	16.5	7.5	27.5
Interview and examination of the patient by physician	28	22.0	12.5	35.0
Total	127*	100.0		

*Degree of physician involvement indeterminate in one patient.

tocols were used, the diagnosis was correct in 16 and incorrect in 2. In one of the two incorrectly diagnosed patients, the nurse practitioner failed to comply with the protocol logic; a diagnosis of urinary tract infection was made even though an insufficient number of leukocytes were present on the microscopic examination. The nurse deviated from the recommended procedure because the patient gave a history of multiple previous urinary tract infections. The urine culture was negative and administration of sulfisoxazole was stopped the following day.

The quality of care rendered by the nurse practitioners is further substantiated by the favorable physician evaluation. Although only 22 percent of the patients were examined, all of the patients' records and prescriptions were signed by a physician. No serious errors of omission or commission were attributed to the nurse practitioners. In 28 patients who were examined by a physician there was 100 percent concordance with the nurse practitioners' physical findings.

Our results indicate that antibiotic use was controlled and minimized by the protocols. None of the 96 patients for whom the vaginitis protocol only was completed received an orally given antibiotic. Metronidazole was appropriately used in patients with trichomonas infections early in the study, but later was replaced with topical therapy. With one exception, as previously described, generic antibiotics were appropriately prescribed for patients presenting with urinary tract symptoms. In no patient was an antibiotic inappropriately withheld or prescribed in the wrong dose.

Most important, patient outcome was highly favorable. Of the patients, 82 percent had alleviation of symptoms. This symptomatic response is very close to that previously reported.[4,5] All patients with culture-proven urinary tract infection had symptomatic response and cure of the infection by the criteria previously discussed.

No serious symptomatic illnesses were missed. Three patients were appropriately referred to the emergency department with correct diagnoses of pelvic inflammatory disease. Foreign bodies in the vagina were detected by the nurse practitioners in two patients. Our data confirm Greenfield's hypothesis that the protocols are conservative in their recommendations and that they can be used safely in an "open" clinic.

Patient satisfaction in this study was extraordinarily high and almost unanimous. We feel that this degree of patient satisfaction is unprecedented, at least at this medical center, and reflects the soundness of this approach to patient care.

Komaroff and co-workers,[4] using these protocols and a urinary tract infection protocol reported that medication costs per visit were virtually the same for nurse practitioner protocol care and routine clinic care. In addition, laboratory costs were 35 percent less with nurse practitioner protocol care than with routine clinic care. Although we did not analyze our data specifically for these costs, our experience with this group of patients would support their conclusions.

Finally, these data confirm that the protocols save time for physicians when used in a walk-in clinic. It is important to empasize that 78 percent of the patients were not examined by a physician and the average physician time per patient was reduced from 20 minutes to 6 minutes. Therefore, true "physician extension" was achieved.

However, because of the longer time spent per patient by the nurse practitioners we were only able to show a 10 percent overall salary cost savings. This figure is less than the salary cost savings shown by Komaroff and co-workers using these protocols and a urinary tract infection protocol.[4] Their reported savings were achieved through a 91 percent reduction in physician time per patient, from 15.5 to 1.4 minutes. We were unable to show this level of physician timesaving.

We feel it is reasonable to conclude that nurse practitioners in the type of clinic studied, seeing patients on the average of two per hour, provide high quality care at a reasonable cost. Some salary cost savings are realized but are not as great as previously reported. The protocols control and minimize antibiotic use and achieve substantial savings in time for physicians.

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Refer to: Rappaport AH, Hoffer PB, Genant HK: Unifocal bone findings by scintigraphy—Clinical significance in patients with known primary cancer. West J Med 129:188-192, Sep 1978

Unifocal Bone Findings by Scintigraphy

Clinical Significance in Patients With Known Primary Cancer

ALLAN H. RAPPAPORT, MD, *San Francisco,* PAUL B. HOFFER, MD, *New Haven, Connecticut,* and HARRY K. GENANT, MD, *San Francisco*

Preliminary findings suggest that in patients with known primary cancer, a large percentage of unifocal lesions seen on radionuclide bone scans are not metastatic. In a survey of radionuclide bone studies done on 861 consecutive patients, 30 patients with known primary cancer had solitary lesions. Adequate follow-up information was available on 21 of these 30 patients. In only four did the lesions prove to be caused by metastatic malignancy.

ONCOLOGISTS increasingly rely on radionuclide bone scans to determine the presence of osseous metastases in patients with malignant disease. It is of utmost importance, therefore, to know whether lesions seen on the scans of such patients are due to metastatic disease. The purpose of our study was to review *solitary* abnormalities seen on bone scan to determine how often these findings were caused by metastatic versus benign lesions.

Patients and Methods

At our institution between July 1, 1974, and June 30, 1975, 861 bone scans were done. All studies were carried out using approximately 15 millicuries of pyrophosphate Tc 99m injected intravenously about three hours before scan. Anterior and posterior whole body images were obtained using either a dual probe 5 inch sodium-iodine crystal rectilinear scanner (Ohio Nuclear 84D) or an Anger camera with scanning table (Searle Radiographics Pho Gamma IV). All scans were interpreted by an experienced physician in nuclear medicine. The clinical report recorded at the time of the study served as the basis for determining if a solitary lesion was present. All bone scan reports for this period were reviewed. All positive reports describing a solitary lesion were selected for further evaluation.

Of all scans, 63 (7.3 percent) showed a solitary lesion. Of these solitary lesions, 30 occurred in patients being evaluated for osseous metastases and serve as the primary study group for this report.

Eighteen of the 30 patients were male and 12 were female. The median age was 60 years with a range of 14 to 82. In 21 of these patients a probable cause of the scan finding was determined by radiograph, laboratory data, biopsy, clinical observation for at least 18 months or a combination of these methods.

In the remaining nine patients follow-up information was inadequate to establish the cause of the positive scan finding. This group included two patients who had undergone radiation or chemotherapy for presumed metastatic disease based on the scan finding and clinical symptoms.

From the Department of Radiology, Section of Nuclear Medicine, and Division of Radiation Oncology, University of California, San Francisco. Dr. Hoffer is now with Yale University School of Medicine.

Submitted, revised, March 23, 1978.

Reprint requests to: Paul B. Hoffer, MD, Department of Diagnostic Radiology, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06510.

Three patients died within one month of scan and no histologic confirmation of the suspected osseous lesion was obtained. In the remaining four patients clinical follow-up was inadequate although in one of these patients with a solitary area of uptake in the humeral head region a diagnosis of "bursitis" was recorded in the clinical record.

Results

The solitary bone scan lesion was proven to definitely represent metastatic disease in only four patients. In 17 patients the lesion proved to be due to an incidental benign disorder (8 patients) or no further evidence was found to confirm a metastatic lesion after a follow-up period of at least 18 months. These results are summarized in Table 1. The bone scans of five of this group of 17 patients are shown in Figures 1 through 5.

Discussion

Radionuclide, skeletal imaging is particularly useful in evaluating the cases of patients with known primary cancer before they undergo definitive therapy. Its popularity has increased as a result of the introduction of effective, low-cost, bone-seeking radiopharmaceuticals, such as pyrophosphate TC 99m and concurrent improvements in imaging equipment.[1]

The greater sensitivity of scintiscans compared with conventional radiographs in the detection of metastatic disease is well documented.[2-6] The percentage of false negative scans in large series was found to be invariably less than 5 percent; for radiographs, the percentage of false negative studies typically exceeded 10 percent. However, despite its greater sensitivity, the bone scan when used alone as an indicator of osseous metastasis lacks specificity.[7-13] It is important to be aware of the lack of specificity of the bone scan because confirmation of metastatic disease frequently alters therapy.

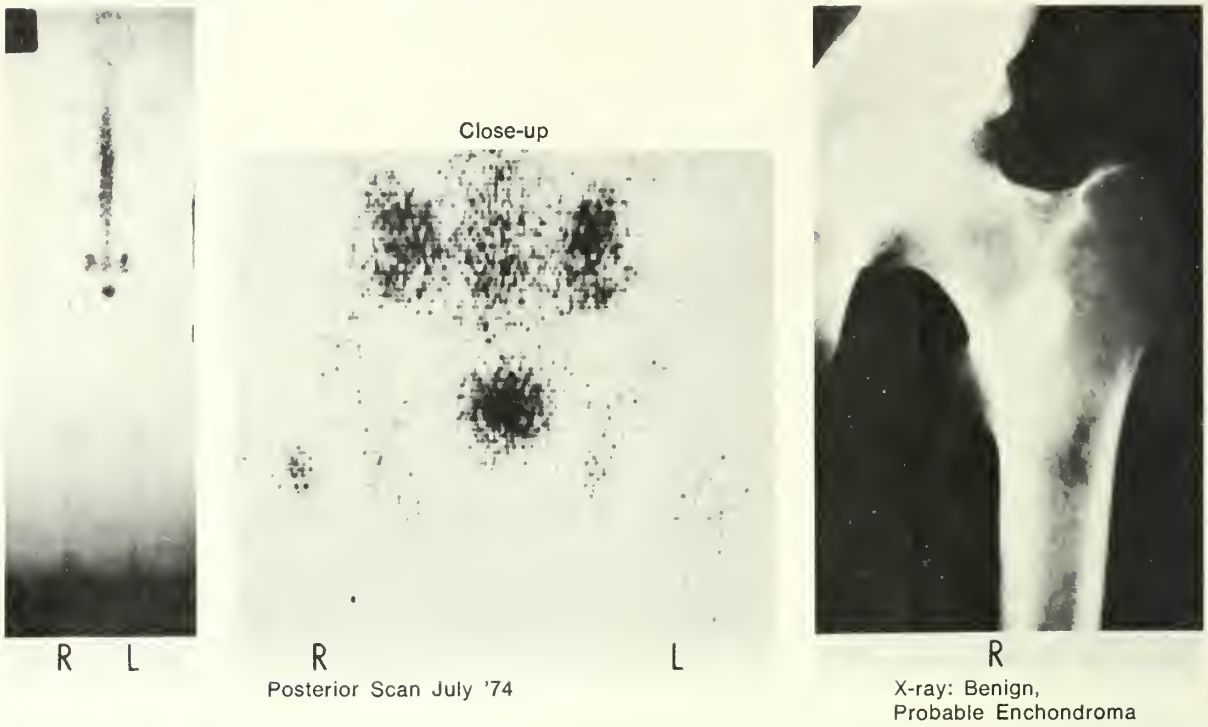
It has been our clinical impression that solitary scan lesions in patients with known malignancy must be carefully evaluated to avoid potentially harmful overstaging. This impression is confirmed by the results of this study. It is often difficult to confirm a specific metastatic lesion in a patient with known malignancy once a presumed diagnosis of metastasis has been made. In our series, however, only four of 21 confirmed solitary lesions were due to metastatic disease. Even if the remaining 9 patients with inadequate follow-up were presumed to have lesions due to metastasis, the overall incidence of positive solitary lesions due to metastatic disease would be 13 of 30 patients, less than 50 percent.

These results confirm the previously reported

TABLE 1.—*Twenty-one Patients With Diagnosis of Malignancy and Solitary Bone Lesion on Scan*

Site of Primary Lesion	*Histologic Diagnosis*	*Site of Positive Scan Finding*	*Cause*
Skin	Malignant melanoma	Right rib	Metastasis
Skin	Malignant melanoma	Left rib	Unknown, no clinical evidence of metastasis 18 months after scan
Skin	Malignant melanoma	L3 vertebra	Paget disease
Skin	Malignant melanoma	Right femur	Enchondroma
Skin	Malignant melanoma	Right foot	Unknown, no clinical evidence of metastasis 18 months after scan
Skin	Malignant melanoma	Left femur	Bone island
Breast	Adenocarcinoma	L3 vertebra	Metastasis
Breast	Adenocarcinoma	Left femur	Bone infarct
Breast	Adenocarcinoma	Right knee	Degenerative disease
Breast	Adenocarcinoma	Costicervical junction	Degenerative disease
Breast	Adenocarcinoma	T9-10 vertebra	Degenerative disease
Lung	Poorly differentiated carcinoma	Left rib	Metastasis
Bone	Osteosarcoma	Left humerus	Metastasis
Hypopharynx	Squamous cell carinoma	Right rib	Unknown, clinically normal 18 months after scan
Hypopharynx	Squamous cell carinoma	Left clavicle	Postsurgical, clinically normal 18 months after scan
Oropharynx	Squamous cell carinoma	Right calvarium	Unknown, clinically normal 18 months after scan
Rectum	Adenocarcinoma	Left rib	Unknown, clinically normal 18 months after scan
Stomach	Adenocarcinoma	Left rib	Unknown, clinically normal 18 months after scan
Brain	Malignant melanoma	Left clavicle	Paget disease
Endometrium	Adenocarcinoma	Left sacroiliac joint	Unknown, clinically normal 18 months after scan
Lymphatic	Well differentiated lymphoma	Right mandible	Unknown, clinically normal 18 months after scan

Dx: MALIGNANT MELANOMA, SKIN
Site: Right Proximal Femur

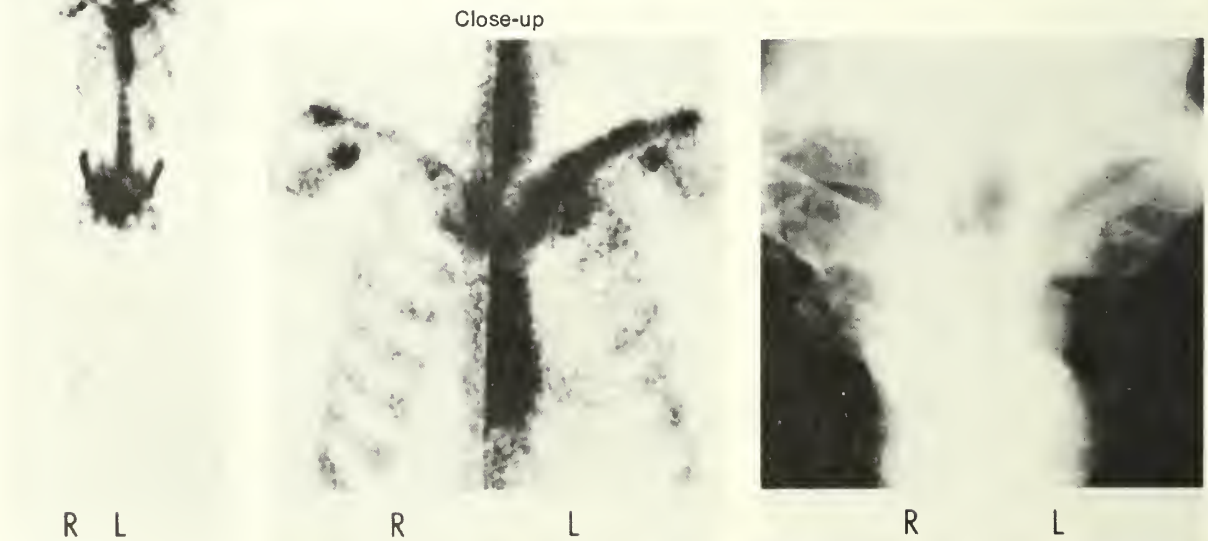


Posterior Scan July '74

X-ray: Benign,
Probable Enchondroma

Figure 1.—Bone scan of a 43-year-old man with malignant melanoma of the skin. A single focus of increased radioactivity is seen in the right proximal femur. The radiograph's appearance typified that of a benign lesion, probably an enchondroma.

Dx: MALIGNANT MELANOMA, BRAIN
Site: Left Clavicle



Anterior Scan May '75

X-ray: Paget Disease

Figure 2.—Bone scan of a 74-year-old man with malignant melanoma of the brain. There is increased activity involving the left clavicle. The radiograph showed cortical thickening, classic of Paget disease.

Dx: MALIGNANT MELANOMA, SKIN
Site: Right Proximal Femur
Close-up

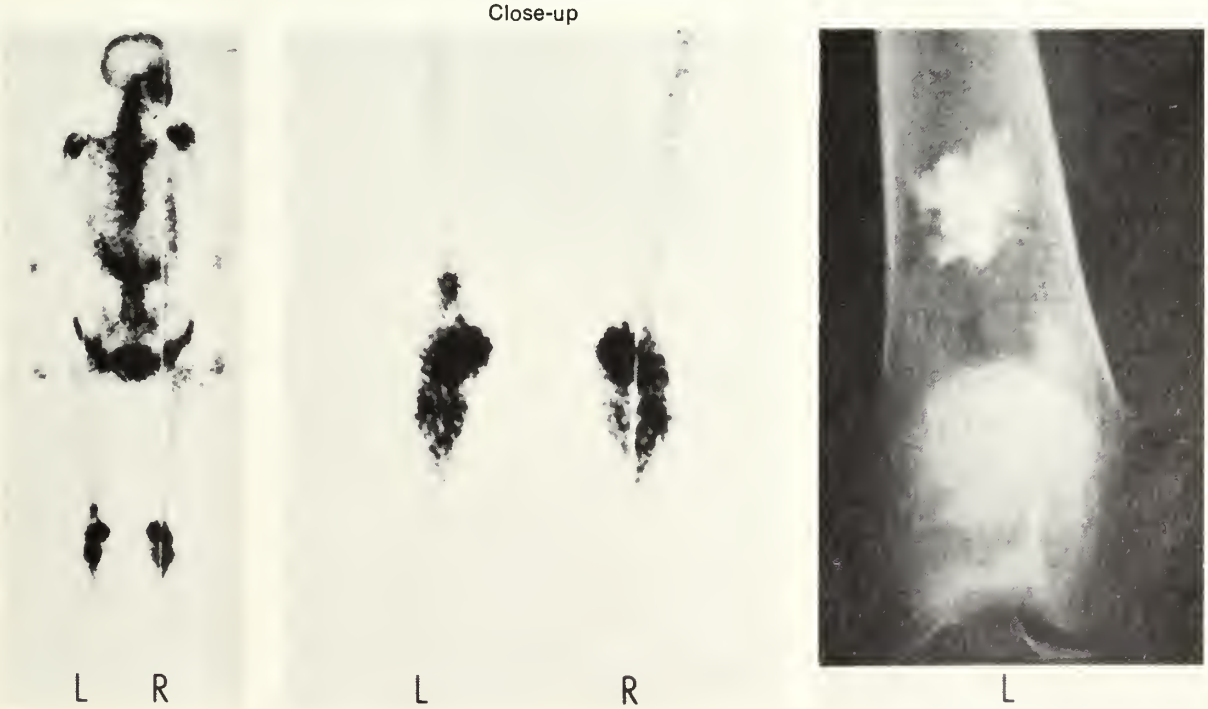
L R L R R

Posterior Scan March '75

X-ray: Bone Island
Pathology: Sclerotic Bone

Figure 3.—Bone scan of a 32-year-old man with malignant melanoma of the skin. A single focus of increased radioactivity is seen in the right proximal femur. The radiograph showed a lesion indicative of a bone island. Biopsy of the area showed sclerotic bone. Because bone islands are not thought to be positive on scan, this unusual case has been separately reported.[14]

Dx: ADENOCARCINOMA, BREAST
Site: Left Distal Femur
Close-up



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Anterior Scan April '75

X-ray: Bone Infarct

Figure 4.—Bone scan of a 67-year-old woman with adenocarcinoma of the breast. A single focus of increased radioactivity is seen in the left distal femur. The radiograph showed a bone infarct.

findings of Corcoran and associates.[15] In their investigation of 172 solitary scan abnormalities they were able to confirm the cause in 90 patients. Only 64 percent of these 90 lesions were due to metastatic disease.

The surprisingly high incidence of benign causes of solitary lesions on bone scan even in patients with known malignancy should *not* discourage the use of the bone scan for early detection of osseous metastasis. Rather it serves to emphasize the importance of attempting to exclude a benign cause for such a lesion once it has been discovered. This can usually be accomplished by noninvasive radiologic or other laboratory methods.

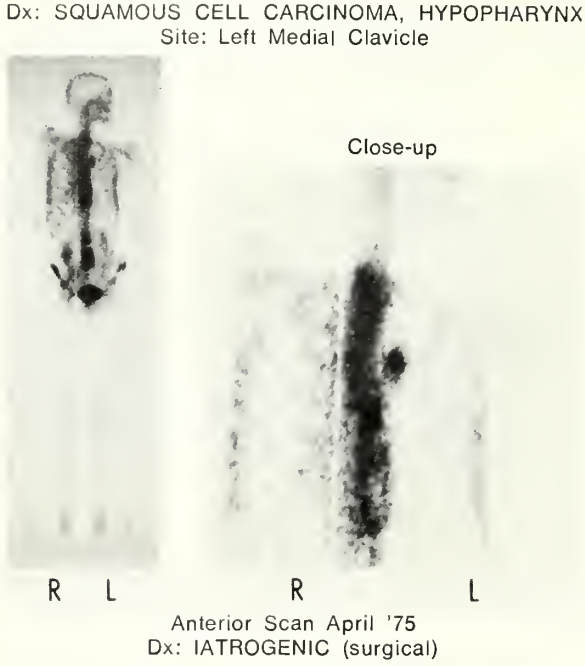

Figure 5.—Bone scan of a 57-year-old man with squamous cell carcinoma of the hypopharynx. A single focus of increased radioactivity is visible in the left medial clavicle. No lesion was seen on the radiograph. In this patient radical dissection of the left side of the neck had been carried out before scanning.

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The Case for Control in Diabetes Mellitus

MAYER B. DAVIDSON, MD, *Los Angeles*

In all diabetic animal models studied to date, microangiopathic complications develop which can be prevented by tight control and reversed by either islet cell transplantation or transplanting the diabetic kidney into a nondiabetic environment. In humans the prevalence of these complications in secondary diabetes mellitus is similar to the prevalence in genetic diabetes. Furthermore, mesangial basement membrane thickness is normal at the onset of the disease and increases shortly thereafter. These two facts strongly suggest that the microangiopathic complications are not an independent genetic component but rather are secondary to the metabolic derangements of uncontrolled diabetes. Normal kidneys transplanted into diabetic recipients developed the vascular lesions of diabetes. Conversely, two diabetic kidneys inadvertently transplanted into nondiabetic recipients showed clearing of the vascular lesions.

Most retrospective studies support the conclusion that control is associated with lessened complications. The three prospective studies published to date also support this hypothesis. Because glucose concentrations cannot be brought to normal levels by present methods, the critical question is whether a major emphasis on restoring metabolism to as nearly normal as possible will help ameliorate the microangiopathic complications in our patients. The accumulated evidence would strongly favor an affirmative answer. Two daily injections of intermediate-acting insulin supplemented with small amounts of short-acting insulin as needed is one method to approach this goal.

In any large diabetic clinic one is struck by the number of patients with devastating complications of diabetes mellitus. Their diabetic control over the years commonly attempted to maintain only 2-3+ urine tests for glucose in order to avoid hypoglycemia. Since the renal threshold for the appearance of glucose in the urine corresponds to a plasma glucose concentration of approximately 200 mg per dl, frequently these patients had glucose levels between 250 and 400 mg per dl much of the time. Can chronic hyperglycemia contribute significantly to the complications of diabetes? The correlation between the usual indices of diabetic control and macroangiopathy is not convincing. However, much evidence is accumulating to suggest that the microangiopathic complications (retinopathy and glomerulosclerosis) can be forestalled or prevented if blood sugar is maintained near normal levels. This review will summarize current evidence, comment on older

From the Department of Medicine, UCLA School of Medicine (University of California, Los Angeles).

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Reprint requests to: Mayer B. Davidson, MD, Department of Medicine, UCLA School of Medicine, Los Angeles, CA 90024.

ABBREVIATIONS USED IN TEXT

BMT = basement membrane thickness
MNCV = motor nerve conduction velocity
PAS = periodic acid-Schiff (staining)

(retrospective) studies which often failed to show correlations between diabetic control and complications, and present an approach to the use of insulin which can be effective in maintaining glucose concentrations at "reasonable" levels (to be defined later).

Studies in Animals

Glomerulosclerosis and retinopathy occur in all animal models of diabetes, whether occurring spontaneously or induced by chemical or viral agents. Specifically, glomerulosclerosis has been documented in alloxan-diabetic monkeys,[1] diabetes spontaneously occurring in dogs[2] or after alloxan or growth hormone administration[3] and rats rendered diabetic with streptozotocin,[4,5] a high sucrose diet[6] or virus inoculation.[7] Retinopathy occurs in streptozotocin-treated rats[8,9] or after a high sucrose diet,[9] as well as in alloxan-diabetic[10] or spontaneously diabetic dogs.[2] Increased basement membrane thickness (BMT) has been found in monkeys with spontaneous diabetes[11] and in alloxan-induced and growth hormone-induced diabetic dogs.[3] Actual basement membrane thickness in spontaneously diabetic monkeys is proportional to the duration of diabetes.[11]

The influence of diabetic control on complications has been studied in dogs made diabetic with alloxan or growth hormone.[12] In 16 diabetic dogs a suboptimal dose of intermediate-acting insulin was given once a day (poorly controlled), as compared with 16 diabetic animals given daily multiple injections of regular insulin based upon the results of glucose determinations throughout the day (tightly controlled). Fifty nondiabetic dogs served as controls. All dogs were followed for five years, which is equivalent to 25 years of human patient follow-up. In the tightly controlled group there developed minimal retinopathy, no cataracts, no glomerulosclerosis by light microscopy, minimal glomerular changes by electron microscopy and a mild increase of muscle BMT over age-matched controls. In the poorly controlled group, on the other hand, there developed definite retinal microaneurysms, hemorrhages and exudates and dense cataracts, in addition to moderate glomerular changes by both light and electron microscopy plus a pronounced increase in muscle BMT.

Approximately six months after diabetes is induced in rats by streptozotocin administration, increased periodic acid-Schiff (PAS) staining occurs in the glomerular mesangium.[4,5] Glycoproteins, an important constituent of basement membranes, are selectively stained by PAS. Therefore, increased PAS staining signifies BMT. These diabetic rats can be treated with pancreatic transplants from syngeneic (genetically identical) nondiabetic litter mates since rejection does not occur. After transplantation, carbohydrate metabolism returns to normal.[5] The increased PAS staining also regresses within several weeks.[5] If a kidney from a normal rat is transplanted into a diabetic litter mate, mesangial basement membrane thickening occurs within several months.[13] Conversely, transplantation of a diabetic kidney into a normal recipient results in clearing of the mesangial changes.[14]

One of the functions of the glomerular mesangium is to take up and clear macromolecules. Macromolecules are taken up normally by the diabetic mesangium but clearing of these molecules from the glomerulus is delayed. Therefore, fluorescent-labeled antibodies directed against various macromolecules will stain glomeruli more intensely when diabetic changes are present. A normal glomerulus shows little or no fluorescent staining. Several months after streptozotocin-induced diabetes, intense fluorescent staining appears in the mesangium[4] which clears after pancreatic transplantation.[5] Additionally, normal glomeruli (with no fluorescent staining) will acquire intense staining on transplantation of the kidney into a diabetic rat.[14]

Decreased motor nerve conduction velocity (MNCV) is characteristic of diabetic neuropathy and can be shown in streptozotocin-induced diabetic rats.[15] When glucose concentrations are returned to normal by twice-daily injections of insulin, MNCV also returns to normal.[15] It should be pointed out that partial lowering of blood sugar has no effect on MNCV.[15]

The following summarizes the animal data: (1) glomerulosclerosis, retinopathy and decreased MNCV occur in spontaneous and chemically-induced diabetes in various species; (2) tight control in dogs retards the development of glomerulosclerosis, retinopathy, cataracts and BMT; (3) tight control in rats restores MNCV to normal;

(4) diabetic glomerular lesions, as evidenced by both increased PAS and immunofluorescent staining of the mesangium, clear after pancreatic transplantation (these changes are induced in normal kidneys placed into diabetic rats); (5) glomerular lesions, as evidenced by increased PAS staining of the mesangium, disappear from the diabetic kidney after renal transplantation into a nondiabetic rat.

Studies in Humans

Those who would argue that the microangiopathic changes of diabetes mellitus are not caused by chronic hyperglycemia have to postulate that these complications follow an independent, but genetically-determined course. If this were true, patients with secondary diabetes mellitus should not show microangiopathic complications. However, the prevalence of both glomerular BMT in patients whose diabetes is secondary to pancreatitis, hemochromatosis or carcinoma[16] and of retinopathy in diabetes caused by hemochromatosis[17,18] is similar to the prevalence in those with genetic diabetes mellitus. By the same token, if the complications follow an independent genetic course, it might be expected that in some patients the microangiopathic changes would be present before the metabolic abnormality occurs. However, glomerular basement membrane width is normal at the time of diagnosis in juvenile-onset diabetes and increases within 1½ to 2½ years.[19]

A strong argument favoring the importance of controlling diabetes is the changes that occur in normal kidneys transplanted into diabetic recipients. Hyalinization (positive PAS staining) of both the afferent and efferent arterioles occurs in only two conditions, cyanotic heart disease and diabetes mellitus. This change, to a moderate or pronounced degree, occurred in all 12 kidneys placed into diabetic patients.[20]* Typical changes of Kimmelstiel-Wilson disease (nodular glomerulosclerosis) were seen in one of the diabetic recipients.[20] In contrast, only three of 28 nondiabetic recipients showed a mild degree of hyalinization (and not of both afferent and efferent arterioles) at a much later time after transplantation.

Immunofluorescent studies were also carried out on posttransplant renal biopsy specimens. Deposition of immunofluorescent material in extracellular membranes of the renal tubule and Bowman capsule, as well as the glomerulus, has recently been shown to be characteristic of diabetic nephropathy.[21] In this study, glomerular basement membranes, tubular basement membranes and Bowman capsules were stained for both albumin and IgG. Notable increases in immunofluorescence to both macromolecules were seen in most kidneys transplanted into diabetic patients, whereas nondiabetic recipients showed only occasional mildly positive immunofluorescent staining.[22] The shorter mean time after transplantation to biopsy in the diabetics (39 months) compared with the nondiabetics (61 months) further highlights these differences in immunofluorescent staining. The converse experiment has also been carried out unintentionally. Vascular lesions cleared completely in two diabetic kidneys within six months after inadvertent transplantation into nondiabetic recipients.[23]

Retrospective studies have served as the main investigative tool to evaluate whether control in diabetic patients will ameliorate the complications. Knowles[24] reviewed 300 such studies from 85 different centers. The conclusions from 50 of these centers were that poor control was positively correlated with vascular disease, 25 concluded that there was no relationship and 10 were undecided. However, Knowles himself felt that most of the reported data were inadequate to serve as a basis for any decision and therefore any association between control and vascular complications was unproven.

A major shortcoming of all the studies is related to the small number of subjects. Therefore, results of two recent studies involving much larger numbers of patients are of special interest. Goodkin[25] followed the cases of 10,538 diabetic persons who applied for life insurance between 1951 and 1970. Mortality was reported at the end of 10, 15 and finally 20 years of investigation. Applicants were classified as poorly or fairly well controlled on their initial examination. Poor control was defined as (1) excessive glycosuria (over 4 percent) or (2) a two hour postprandial blood glucose value over 250 mg per dl or (3) a history of a recent high blood glucose level or (4) a history of severe insulin reaction or onset of diabetic coma after the initial period of observation. The mortality of the poorly controlled group was approximately 2½ times that of the fairly well controlled patients. This difference persisted despite the fact that a larger proportion

*The published data indicate 11 of 12. Dr. Mauer described the appearance in the 12th patient at a talk given to the American Diabetes Association, Southern California Affiliate, in the spring of 1977.

of younger diabetics appeared in the poorly controlled group. Another study involved 4,400 diabetics whose indices of nephropathy, neuropathy, retinopathy and control were evaluated at least once a year for up to 20 years.[26] The incidence and prevalence of these three complications ran a parallel course and were closely related to control as well as duration of the diabetes.

A unique retrospective study was published in 1960. Johnsson[27] compared the prevalence of retinopathy and nephropathy in two series of diabetics. Series I contained all patients whose diagnosis of diabetes was made before the age of 40 in Malmö, Sweden, between 1922 and 1936. During this period attempts were made to keep the urine sugar-free by strict diet and short-acting insulin, the only preparation available. Series II contained all patients diagnosed between 1936 and 1945, during which period long-acting insulin became available. At this time, diet was liberalized and the importance of glycosuria was belittled as long as the patients had no polyuria or ketonuria. Series I contained 71 patients, 17 of whom were excluded from the study because they did not survive long enough to permit evaluation of the effect of treatment. Series II contained 115 patients, 10 of whom were excluded for the same reason. At the time of review, records of the remaining 54 patients in series I and 105 patients in series II were available for analysis. Thirty-five of the patients in series I and 100 in series II were alive and could be questioned and examined. For the most part, the principles of treatment followed initially by series I patients were maintained after 1936. Frequent insulin reactions were much more common in series I patients, providing indirect evidence of tighter control. Nephropathy was diagnosed when proteinuria was present in more than half of all examinations during the preceding year. After 15 years of diabetes in both groups, nephropathy was seven times more prevalent in series II. The prevalence of advanced retinopathy was also increased sixfold in series II patients in spite of the fact that at the time of review the mean duration of diabetes was 15.9 years compared with 26.5 years in series I.

Three recently published prospective studies also support a role for control in favorably affecting the development of diabetic complications. In a Japanese study[28] serial renal biopsy studies were done on 23 patients whose fasting plasma glucose levels were measured every two weeks or more frequently. Good control was defined as values never greater than 120 mg per dl, poor control as values greater than 150 mg per dl on "all or many occasions" and fair control as falling in between. The amount of PAS staining in the biopsy studies was evaluated independently by three nephrologists who had no knowledge of the clinical course. Of 13 patients with poor control, 10 showed progression of their nephropathy. Three of four with fair control also showed progression while none of the six patients with good control showed progression. The duration of diabetes at the time of the first biopsy (approximately 4½ years) and the follow-up period (approximately four years) were similar in the patients showing progression and nonprogression. The age (years ± SEM) of onset of diabetes in those 13 patients whose nephropathy progressed was significantly lower (36.3 ± 3.9) than in the 10 patients who showed no progression (52.6 ± 1.9). However, these results do not support the supposition that good control and relative absence of glomerulosclerosis are associated only because the person with adult-onset diabetes, with less severe alteration of carbohydrate metabolism, also may have an independent genetic constitution which is less likely to lead to nephropathy. Two of the four persons with adult-onset diabetes with poor control in this study showed progression of their renal lesions.

In another Japanese study,[29] the progression of retinopathy was correlated with fasting blood glucose levels over six years in 356 diabetic patients (mostly maturity-onset). Good control was defined as at least 80 percent of the fasting glucose levels less than 140 mg per dl, poor control as more than 50 percent of the fasting glucose concentrations exceeding 170 mg per dl and fair control as lying in between. Retinopathy was graded at least once per year after bilateral dilation of the pupils and examination with magnifying lenses by an ophthalmologist who had no knowledge of the metabolic status of the patient. Two, four and six years after the study began, the percent of eyes in which new lesions appeared and old lesions progressed was lowest in the group with good control, midway in the patients with fair control and highest in those with poor control. Conversely, the percent of eyes in which old lesions improved was highest in the group with good control, intermediate in those with fair control and lowest in the group with poor control.

The final prospective study to be considered comes from France.[30] Fifty-two patients with the

TABLE 1.—*Microaneurysms in Diabetic Patients Receiving Single or Multiple Injections of Insulin**

Microaneurysms (mean±SEM)	*Single Injection*	*Multiple Injection*	*p*†
Base line	12.7±3.5	9.0±3.3	NS
Last examination	33.0±7.9	15.2±4.9	<.05
Difference	20.3±4.9	6.2±2.5	<.02
Increase/year	7.2±1.9	1.8±0.7	<.02

*Data from reference 30.

†Student's t test between means. Significance accepted at the .05 level.

TABLE 2.—*Joslin Clinic Criteria for Control of Diabetes**

Time	*Good*	*Fair*	*Poor*
Fasting	125 (110)	150 (130)	All others
One hour postprandial	170 (150)	205 (180)	
Two hours postprandial	150 (130)	170 (150)	
Three hours postprandial	125 (110)	150 (130)	

*At least 70 percent of all plasma (whole blood) glucose levels (mg/dl) must be less than the listed value in order for that degree of control to be designated.

following characteristics were entered into the study: (1) less than 60 years of age, (2) treatment with less than 80 units of intermediate-acting insulin injected once per day, (3) no life-threatening disease other than diabetes, (4) known reliable outpatient attendees and (5) an early stage of simple (not proliferative) retinopathy in the more diseased eye. Annual fluorescein angiopathy of the posterior pole was done and the number of microaneurysms quantitated. The patients were randomly allocated into two groups, one to continue receiving one injection of insulin per day and the other to receive multiple doses of insulin. The base line characteristics of the two groups were similar including duration of diabetes, age at both diagnosis of diabetes and at onset of the trial, daily dose of insulin, urinary sugar (grams per 24 hours) and fasting blood sugar. Ten patients were lost to follow-up during the first year but these dropouts did not differ in base line characteristics from the remaining subjects. The cases of 21 patients in each group were followed for one to four years with a mean duration of 34.9 months for the single injection group and 38.1 months for the multiple injection group. Most of the patients in the latter group received intermediate-acting insulin before breakfast and dinner. The average fasting blood and 24 hour urinary sugar during the trial was less (but not significantly so) in the multiple injection group. During the last year, however, the decrease from the base line values of both fasting blood glucose and urinary glucose was significantly greater in the patients receiving multiple injections of insulin. Associated with this improvement in control, the increase in the number of new microaneurysms was several times less than in the single dose insulin group (Table 1).

The following summarizes the human data: (1) the prevalence of retinopathy and glomerulosclerosis in secondary diabetes is similar to the prevalence in genetic diabetes, (2) glomerular basement membrane width is normal at the onset of juvenile-onset diabetes mellitus and increases progressively after approximately one year, (3) diabetic vascular changes appear in nondiabetic kidneys transplanted into diabetic recipients, (4) vascular lesions of diabetic kidneys clear after transplantation into nondiabetic recipients, (5) studies utilizing a very large number of patients show a correlation between fewer complications and good control, (6) a comparison of two different principles of treatment (multiple shots of short-acting insulin and strict diet versus one injection of long-acting insulin and free diet) show a manyfold decrease in glomerulosclerosis and severe retinopathy under the regimen that should have resulted in tighter control and (7) in three prospective studies, less progression of glomerulosclerosis and retinopathy is associated with indices of better control.

There is no doubt, however, that many retrospective studies utilizing up to several hundred patients each have failed to show any correlation between diabetic control and complications. In my view, the main reason for this is the degree of control that is usually attained by present methods of treatment. The criteria used by the Joslin Clinic, an outspoken advocate for strict control, are listed in Table 2. Given the present state of the art, I doubt whether very many patients can be maintained in good control. Only 15 percent of diabetic patients whose cases were followed by the Joslin Clinic fall into that category.[31] Therefore, correlations are being sought in patients whose control ranges between fair and poor. It takes years for complications to become clinically manifest and during this period diabetic control can vary considerably. Furthermore, a single glucose concentration or even a 24-hour urinary glucose measurement is probably not an accurate indication of the patient's control during the weeks preceding the test. Therefore, it seems unrealistic to expect that differences in complications can be seen in the small number

of patients usually studied whose control over time can not be evaluated very well and may not differ very much within the group.

There are two other situations which are not in accord with the data correlating good control with delayed development of complications. An occasional patient may present with renal disease secondary to glomerulosclerosis whose glucose tolerance is only mildly abnormal or possibly within normal limits.[32-34] The explanation usually advanced is that undiscovered, probably intermittent, hyperglycemia has been present in these patients for varying periods of time before their renal disease became manifest. A less likely possibility is that there are other causes of the renal lesions which mimic those of diabetic glomerulosclerosis.* At present, both of these tenets are obviously impossible to prove or disprove. Conversely, there are occasional patients with a long history of diabetes whose control over the years by almost any criteria would be considered poor and who have no proteinuria and minimal retinopathy and neuropathy. These few patients serve to remind us that there may be other factors impinging on the development of diabetic complications, but in my opinion they do not effectively blunt the weight of evidence presented.

Controlling Insulin-Dependent Diabetic Patients

The glucose concentrations in nondiabetic persons range between 80 and 120 mg per dl throughout the day and microangiopathic lesions do not normally occur. In diabetic animals, changes consistent with glomerulosclerosis, retinopathy and neuropathy can be prevented or reversed if nearly normal metabolic conditions can be reestablished. Until the artificial pancreas or pancreatic transplants become feasible in humans, glucose levels in diabetics will remain significantly above normal. Therefore, given our present ability to control blood glucose levels in diabetic patients, the crucial question is whether complications can be ameliorated in patients whose glucose concentrations can be consistently kept between approximately 120 and 250 mg per dl 24 hours a day over many years as compared to patients whose glucose levels consistently range between 200 and 400 mg per dl. This question is probably untestable (at least in humans) but given the evidence presented in this article, the conclusion that the tighter degree of control will be helpful seems warranted.

*It was recently reported that two patients with normal glucose tolerance thought to have diabetic glomerulosclerosis by light microscopic criteria really had other causes of renal disease when electron microscopic and immunofluorescent studies were utilized.[36]

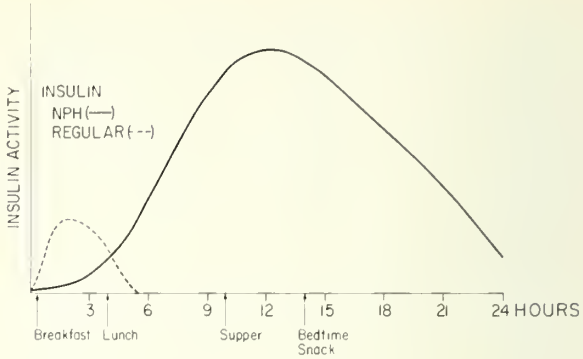

Figure 1.—Time-course of action of one injection of insulin per day (see text for description).

If one accepts that tight control is advisable, how can it be accomplished? Figure 1 shows the usual time-course of the activity of insulin injected before breakfast. Intermediate-acting insulin (NPH or lente) is represented by the solid curve. There is usually a lag period of two to four hours before enough is absorbed to have a measurable effect. The peak activity occurs around supper (8 to 12 hours after injection) and the duration of the effect is approximately 24 hours. Because of the delayed absorption, hyperglycemia often occurs after breakfast. To prevent this, a small amount of short-acting insulin (regular or crystalline zinc insulin represented by the dotted line) can be mixed with the intermediate-acting insulin in the same syringe. This insulin, which is absorbed rapidly, starts to work within 15 to 30 minutes, peaks at one to two hours but may show some effect for up to four to six hours. To prevent hyperglycemia, this single injection has to cover breakfast, lunch and dinner calories as well as a bedtime snack and also provide enough insulin to control hepatic glucose production throughout the night. Two response patterns are seen. Most commonly, the appropriate amount of intermediate-acting insulin to achieve satisfactory control during the day is not enough to prevent fasting hyperglycemia the following morning. Less often, the appropriate amount of intermediate-acting insulin for daytime needs is too much during the night and hypoglycemia occurs. In the first situation, hyperglycemia is present during much of the night. In the second pattern hyperglycemia occurs throughout much of the day since the amount of inter-

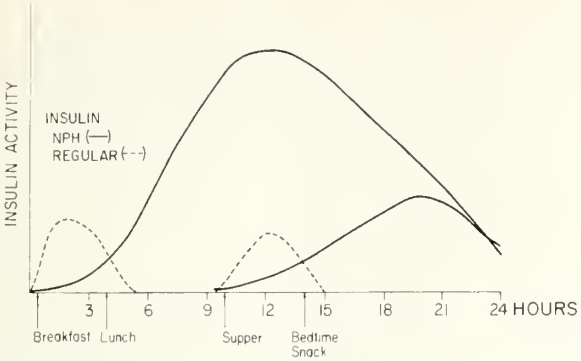

Figure 2.—Time-course of action of two injections of insulin per day (see text for description).

mediate-acting insulin has to be decreased to avoid nighttime hypoglycemia.

Two injections a day can eliminate this problem. The usual time-course of the activity of insulin given before breakfast and before supper is shown in Figure 2. The total insulin activity for any period is the sum of all of curves operating at that time. The effectiveness of the morning intermediate-acting insulin is best judged by the before supper test, the evening intermediate-acting insulin by the before breakfast test, the morning short-acting insulin by the before lunch test and the evening short-acting insulin by the before bed test (Table 3). In practice, the appropriate amount of *intermediate-acting insulin is established first before short-acting insulin is added.* The morning and evening doses are regulated independently of each other by monitoring the appropriate urine or blood test. In this manner, approximately 75 percent of the dose is administered in the morning and 25 percent before supper. Only when the proper amount of intermediate-acting insulin is decided upon are the before lunch and before bed tests used to determine if small amounts of additional short-acting insulin are necessary.

I usually start a thin diabetic person on a regimen of 15 units of intermediate-acting insulin before breakfast and 5 units before supper. These doses are then adjusted by increments of 5 units as the results of appropriate urine or blood tests indicate (see Table 3). The initial amounts for an obese diabetic person would be 30 and 10 units, respectively. Once the results of fasting and before supper tests are satisfactory, attention is directed to the before lunch and before bed tests. Five units of short-acting insulin are added to either or both injections of intermediate-acting insulin as required. Usually 5 to 10 units of regular insulin at each time are all that is necessary

TABLE 3.—*Timing of Most Appropriate Test to Judge Effectiveness of Insulin Injections*

Insulin	*Test*
Intermediate-acting, before breakfast .	Before supper
Short-acting, before breakfast	Before lunch
Intermediate-acting, before supper ...	Before breakfast
Short-acting, before supper	Before bed

(at least in thin diabetic persons). Larger amounts will often cause greater swings in glucose levels and may make control more difficult.

What reasonable goals can be attained with this regimen? Fasting plasma glucose concentrations below 150 mg per dl and postprandial levels below 200 mg per dl are possible to achieve in some patients. Most patients will be able to maintain fasting glucose values below 180 mg per dl and postprandial ones below 250 mg per dl. The postprandial glucose concentration will also depend on the amount of simple carbohydrate ingested as well as the temporal relationship between eating and blood sampling. Thin, well-motivated patients whose daily routine does not include an inordinate amount of stress are more likely to achieve better control. The premise here is that patients whose glucose levels never exceed 200 to 250 mg per dl will fare better in regard to complications than patients whose glucose values are often over 300 mg per dl. As discussed above, this postulate can not be rigorously proven but the available evidence from both animal and human studies strongly suggest that it is true.

Addendum

Two abstracts presented at meetings of the American Diabetes Association bear on this article.

Fluorescein leakage into the eye was increased 2.5 times in diabetic rats compared with controls. Two weeks following islet cell transplantation, the fluorescein accumulation returned completely to normal.[35] More chronically, the eyes and kidneys of diabetic rats and those relieved of their diabetes with whole pancreas transplants were compared one and two years after transplantation. Diabetic changes were notably reduced in both of these organs in the transplanted animals.[37]

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Specialty Conference

Participants

TIMOTHY G. CANTY, MD
PHILIP GOSCIENSKI, MD
DAVID EDWARDS, MD
SANDRA DALEY, MD
WILLIAM L. NYHAN, MD, PhD

From the Departments of Surgery, Pediatrics and Radiology, University of California, San Diego, University of California Medical Center, San Diego, and Naval Regional Medical Center, San Diego.

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Staphylococcal Pneumonia

WILLIAM L. NYHAN, MD, PHD:* *The conference centers on a problem which was not long ago epidemic among pediatric populations. It is less common today, though still with us. The patient will be presented by Dr. Daley.*

SANDRA DALEY, MD:† The patient, a 10-month-old boy, was well until one week before admission when he presented with chief complaints of fever, progressive cough, respiratory distress and pronounced irritability. He was given three intramuscular injections of ampicillin by a physician before coming to the emergency room because his symptoms had become worse. He was promptly admitted to hospital.

On physical examination the infant was noted to be thin, pale, mildly cyanotic and in moderate respiratory distress. His weight was in the third percentile, length in the 25th percentile, and head circumference in the 10th percentile. Positive physical findings were limited to the chest. He had sternal retractions. There were tubular breath sounds with loud rhonchi and moist rales at the right base. Laboratory evaluation showed a leukocyte count of 29,500 per cu mm with 75 percent segmented neutrophils, 4 percent bands, 13 percent lymphocytes and 8 percent monocytes. Hematocrit was 33 percent and platelet count was 720,000 per cu mm. Clotting studies gave findings within normal limits. The sedimentation rate was 30 mm per hour. Lumbar puncture showed no abnormalities. Assay of the arterial blood gases while the baby was breathing room air showed a pH of 7.56, an oxygen pressure (Po_2) of 52 and a carbon dioxide pressure of 30 mm of mercury and base excess of −4. Gram stain of the sputum showed Gram positive cocci and rare polymorphonulear cells. Roentgenogram of the chest showed a right hydropneumothorax without significant shift of the mediastinum. There was partial collapse of the right lung.

The patient was given 40 percent oxygen by mask and a number 20 chest tube was inserted. Air and 60 ml of turbid, tenacious yellow fluid were removed. Gram stain of a smear of the pleural fluid showed Gram positive cocci in clusters and chains. Treatment was started with intravenous administration of oxacillin, ampicillin and gentamicin, but when the 48-hour culture of the pleural fluid confirmed the findings on smear of the presence of a penicillinase-positive Staphylococcus aureus, ampicillin and gentamicin were discontinued. On the sixth hospital day the patient was breathing room air. On the 11th day the chest tube was removed, and culture of the tip showed no growth. On the 19th hospital day the infant appeared remarkably well. Intravenous ad-

*Professor and Chairman, Department of Pediatrics.

†Pediatric resident.

Reprint requests to: Timothy G. Canty, MD, Div. of Pediatric Surgery, University of California Medical Center, P.O. Box 3548, San Diego, CA 92103.

ministration of oxacillin was discontinued, and dicloxacillin was given orally for three more weeks.

The patient has been seen several times in the Primary Care Clinic for follow-up and has done very well. Some residual changes still are present on x-ray films of the chest.

DR. NYHAN: *Let us turn to Dr. David Edwards who will present and discuss the roentgenographic findings.*

DAVID EDWARDS, MD:* The initial chest films obtained in the emergency room were anteroposterior, lateral and decubitus views (Figures 1, 2 and 3). The left lung showed vascular congestion but was otherwise normal. The right hemithorax contained no visible pulmonary parenchyma. Instead it was filled with large collections of free-flowing fluid and free gas that produced the gas-fluid levels seen on the gravity-dependent views.

*Assistant Professor of Radiology and Pediatrics.

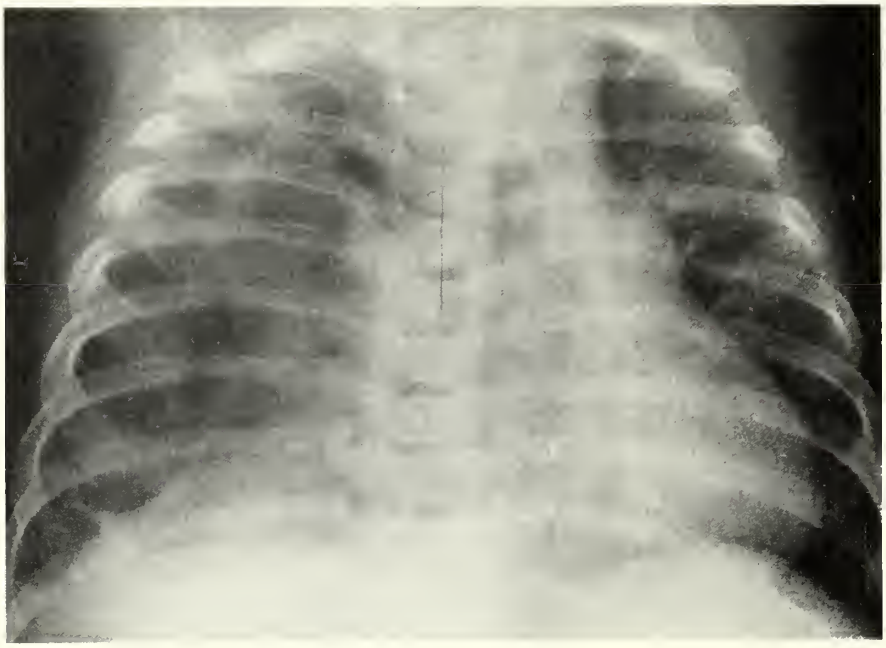

Figure 1.—Initial radiograph: anteroposterior view of chest with patient supine.

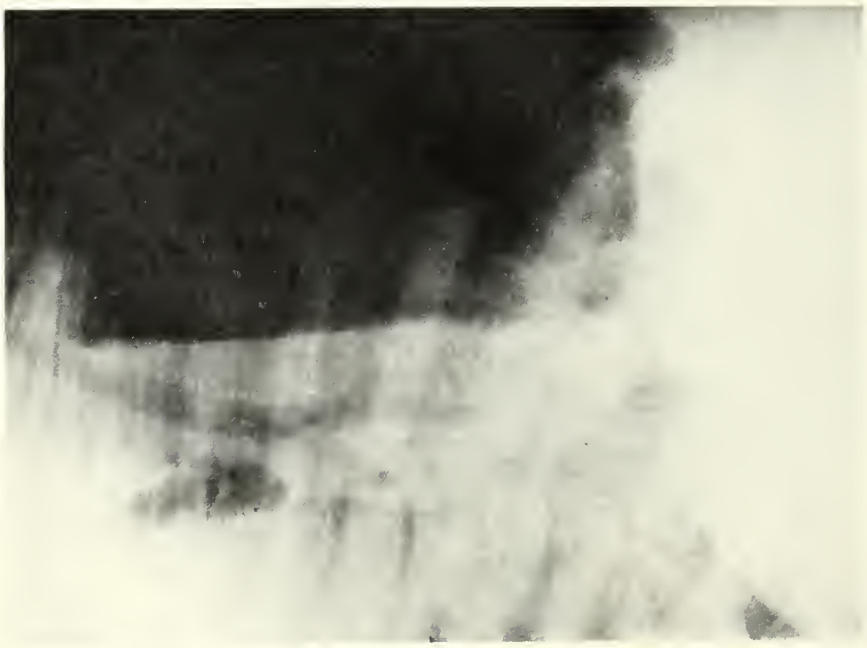

Figure 2.—Initial radiograph: cross-table lateral view of chest. Note large gas-fluid levels.

This most likely represents a hydropneumothorax with loculated areas. One could also see this picture with giant bullae containing fluid.

The differential diagnosis of pneumothorax in children is a large one. The most common cause is related to assisted ventilation, with or without preceding interstitial or mediastinal emphysema. Pneumothoraces from trauma are also common, including such trauma as surgical operation and thoracentesis. So-called spontaneous pneumothoraces are relatively uncommon in children. Other less common causes include chemical (hydrocarbon) pneumonitis, pneumonia, ruptured pneumatocele, a bronchopleural fistula from lung abscess or granulomatous disease, and lung infarcts such as those seen in sickle-cell disease. Certain underlying diseases may predispose to pneumothorax, including cystic fibrosis, bronchopulmonary dysplasia, meconium aspiration, eosinophilic granuloma and neoplasms such as metastatic osteogenic sarcoma. The appearance of multiple cystic-appearing lesions in the chest may suggest a diagnosis such as diaphragmatic hernia, sequestration or cystic adenomatoid malformation.

There are actually a wide variety of infectious causes for an x-ray film of the chest that appears like this. Of the many organisms that produce cysts or cavities in the chest, Staphylococcus aureus is certainly the most common. However, many other bacteria, especially Klebsiella and tuberculosis, can do this. Fungal organisms, especially Coccidioides, Histoplasma, Actinomyces and Nocardia must also be considered. Of parasitic agents, amoeba might be expected to be seen in the San Diego area; lung flukes and hydatid cysts would be very uncommon.

It is worth emphasis that the apparent cystic structures seen in acute staphylococcal pneumonia are seldom pneumatoceles, that is, holes in the pulmonary parenchyma. They are usually air bubbles within an empyema. Occasionally they may represent subpleural emphysema. There is histological evidence that air may dissect along interstitial pathways to accumulate beneath the pleura.[1] In either of these situations it would be easier to explain how a lung that looks disastrously riddled with holes can rapidly return to normal. We have also seen patients with respiratory distress syndrome and interstitial emphysema in whom large pneumatocele-like structures have developed that appeared and disappeared with great rapidity. These are most likely subpleural emphysema. In the patient we are discussing here, one must speculate that at some point the pleura ruptured, leading to a pneumothorax.

Following insertion of the chest tube the right lung rapidly reexpanded (Figure 4), although considerable pleural fluid persisted for several

Figure 3.—Initial radiograph: left lateral decubitus view of chest. Again, large gas-fluid levels are present in the right hemithorax.

days. It was clear that air pockets seen were not subpleural because of the rapidity with which they came out through the chest tube. Our most recent x-ray film of the chest in this patient, done 37 days after admission, showed right-sided pleural thickening and minimal residual parenchymal abnormality in the right lung. Considering the initial findings, the return toward normal was striking.

DR. NYHAN: *Our next speaker, Dr. Philip Goscienski will discuss the problem from the medical point of view.*

PHILIP GOSCIENSKI, MD:* I would like to begin by calling attention to a comment made by Dr. William Osler many years ago: "Keep an open mind toward pneumonia. Our grandchildren will be interested and are likely to have as many differences of opinion as we have."[2] I could not help thinking how that admonition applies to childhood pneumonias. Once the etiologic agent is identified, then differences of opinion are not as pronounced, although even such a simple concept of how best to drain an empyema is occasionally the subject of argument. I would like to make a few background comments on the general subject.

Staphylococcal disease tends to be cyclic in nature, just as do most other infectious diseases. Cycles of staphylococcal disease have a periodicity of something on the order of about 25 years. We are probably just emerging from one now. The Staphylococcus is not, in fact, a single pathogen but a family of pathogens with widely varying potential for causing illness. Serologic techniques such as precipitin and agglutination methods are not as useful as in the case of salmonellae or pneumococci. Bacteriophages are often helpful tools for classifying staphylococci. If the strain of Staphylococcus can be lysed by bacteriophages 80/81 we call it an 80/81 strain.

There are several prominent phage groups, and there is a tendency (Table 1) for certain strains to produce more or less severe illness. Some colonize persons and virtually never produce illness. For example, strain 80/81 causes severe illness in infants and other susceptible groups and may cause disease in almost anyone whom it happens to colonize. On the other hand, bullous impetigo, which is caused by strains 3A and 3B, occurs exclusively in early infancy. The same strain may cause toxic epidermal necrolysis in older children, whereas a phage type such as strain

*Chief, Pediatric Infectious Disease Division, Naval Regional Medical Center, San Diego.

TABLE 1.—*Invasiveness** of *Strains of Staphylococcus Aureus*

Phage type 80/81
Severe illness in infants and other susceptible groups
Phage type 3A/3B
Bullous impetigo
Phage type 502A
A "benign" strain in normal hosts

*Tendencies, not fixed characteristics.

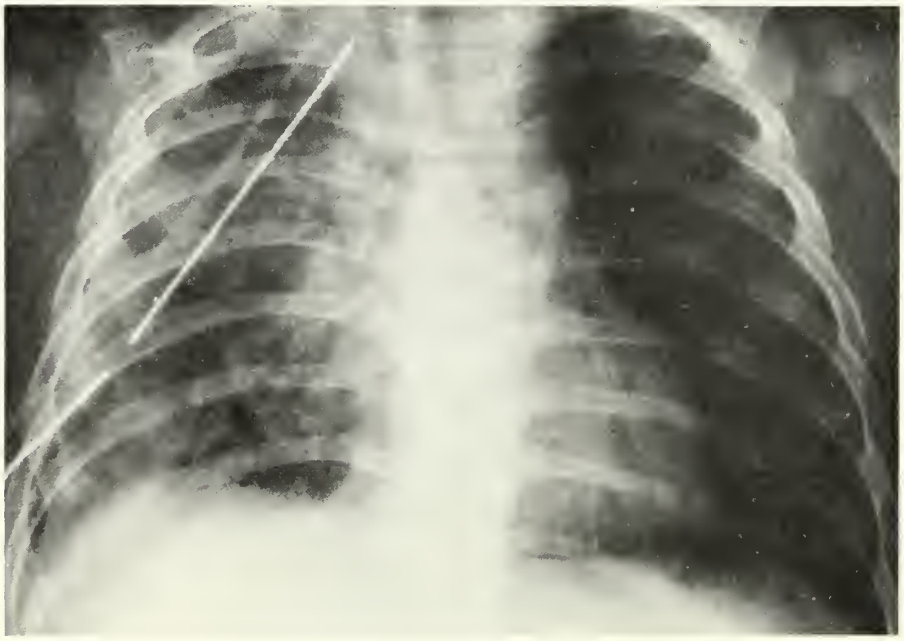

Figure 4. — Anteroposterior view of chest with patient supine following chest tube insertion. The right lung has expanded notably after removal of considerable gas and fluid.

502A is a benign strain in virtually everyone. Phage type 502A may cause severe illness in a child with an unusual predisposition towards bacterial infection.

Over the years there has been a changing incidence of certain pathogens which have a potential for causing empyema. Before antibiotics became available the Pneumococcus was responsible for most cases of empyema. During the late 1940's when sulfonamides and penicillin became available the incidence of pneumococcal empyema declined dramatically. The Staphylococcus was emerging at that time, perhaps as a prelude to the pandemic which occurred in the 1950's. By 1963 most cases were due to the Staphylococcus.

Staphylococcal pneumonia is often a rapidly progressive disease in infancy. It constitutes a true pediatric emergency. It may be preceded by a simple upper respiratory infection, conjunctivitis or an abscess in another part of the body. Early symptoms may be somewhat misleading. About 50 percent of the patients have significant gastrointestinal symptoms such as vomiting, diarrhea and abdominal distention. In the absence of staphylococcal lesions elsewhere, clinical diagnosis has to be based on suspicion of the disease, especially in a very young infant. Severe pneumonia in the first year of life is very likely to be due to the Staphylococcus. An abrupt change in the course of an upper respiratory infection is a not uncommon finding in staphylococcal pneumonia. Changes seen on x-ray studies may be virtually pathognomonic. A diagnostic aid which is often overlooked in young infants is the examination of the gastric contents. Heinz Eichenwald, MD (personal communication, 1974) has observed that a Gram stain of the gastric contents may show large numbers of Gram positive cocci. The culture is also positive. If the child is poorly nourished, Staphylococcus aureus may be a likely cause of a pneumonia. Mimica[3] reported from Santiago on the results of 543 diagnostic lung taps. A high yield of staphylococci appeared to be associated with the poor nutritional status of most of his patients. It would be convenient if a diagnosis of staphylococcal disease could be based on a throat or nasopharyngeal culture, but it cannot because up to 50 percent of normal persons are colonized with Staphylococcus aureus. Even a lung tap in a patient who does not have a pleural effusion has limited usefulness. Gram-stained smears made from needle aspirates of the lung are usually not diagnostic and the culture will be of no help for another 24 hours or more. Staphylococcal pneumonia is an urgent, serious problem. One cannot wait for the results of a culture to initiate definitive therapy.

Antibiotic therapy should be fairly straightforward. Orally given antibiotics are never indicated for severe staphylococcal illness. Dosages recommended by the manufacturers for almost all of the semisynthetic penicillins are too low. For example, in 1975 the recommended dose for methicillin was 100 mg per kg of body weight per day whereas most pediatric authorities recommend 400 mg per kg per day. The dosage recommended by Krugman and Ward[4] for oxacillin was 50 to 100 mg per kg per day but I would feel that a dose of 200 mg per kg per day is more appropriate.[5] Kanamycin alone is never a good choice for staphylococcal infection but combined with erythromycin it may be used for patients who have a serious allergy to penicillin. Methicillin is not identical to other semisynthetic penicillins. It is a useful agent, but it may be limited by the occurrence of interstitial nephritis in patients receiving large doses over long periods. Unfortunately patients with staphylococcal pneumonia or osteomyelitis require large doses over long periods. Oxacillin or other isoxazolyl derivatives are used most commonly. I do not feel there is enough difference in utility among such agents as cloxacillin, dicloxacillin and nafcillin to warrant special discussion. Cephalosporins are almost never the primary drugs of choice in most pediatric infectious diseases. They may be effective against penicillin-resistant staphylococci in clinical situations which are clearly not life-threatening. Vancomycin should be considered only because we occasionally see a patient who is not only allergic to the penicillins and their derivatives but to cephalosporins as well. Vancomycin is a rather toxic drug, causing nephrotoxicity, ototoxicity and phlebitis and for these reasons it cannot be our first choice but it may be lifesaving on occasion. Bacitracin was used successfully in the treatment of some patients with staphylococcal pneumonia. It was used commonly during the 1950's when penicillin-resistant staphylococci were becoming widely prevalent, and the penicillinase resistant penicillins had not yet been developed.

Gentamicin must be discussed but it is never a first choice. Consideration of the history of kanamycin in staphylococcal infection may provide some perspective. Kanamycin was used dur-

ing the 1950's because there were *in vitro* data from the laboratory indicating that it should be effective against staphylococci. Unfortunately patients treated with kanamycin alone did poorly. When gentamicin became available data from the laboratory again indicated that the Staphylococcus was susceptible. It was not used clinically because of experience with kanamycin. However, it has been found that gentamicin is relatively useful for staphylococcal disease, although there are almost always better choices.

The duration of therapy should be adjusted to the needs of the patient and the severity of the illness. Generally we feel that treatment should continue for at least three weeks and that most of that course should be by the intravenous route. Recurrence of staphylococcal disease is a well recognized phenomenon. Small numbers of organisms, which are called persisters, localize in foci of necrosis where they are protected from the cellular and humoral defense mechanisms of their host.

DR. NYHAN: *We have felt in general in the treatment of serious infections due to Staphylococcus aureus that vigorous antibacterial treatment should be continued until the main signs of infection are gone, rather than to select some arbitrary number of days or weeks. Thus an empyema should have stopped draining and there should be no obvious pus and the patient's temperature, leukocyte count and sedimentation rate should be normal. We generally continue treatment for 7 to 14 days thereafter.*

The accumulation of pus is a characteristic of staphylococcal infections. The presence of pus is an absolute indication for surgical intervention. Let us turn the discussion to Dr. Canty for a consideration of surgical treatment.

TIMOTHY G. CANTY, MD:* I will take this opportunity to talk about the use of chest tubes in general, in addition to their use in empyema. Discussion of their use in empyema can simply be summed up by saying that they must indeed be used in empyema. Chest tubes, along with chest suction and chest bottles, remain a mystery to most if not all medical students and a good number of residents and practicing physicians. Physicians who use these instruments sometimes do not really know why they do what they do and really how to manage them.

*Assistant Professor of Surgery; Chief, Division of Pediatric Surgery.

A chest tube is essentially nothing more than a fancy drain. It is, however, a unique drain, put in a very special place, the thoracic cavity. It is usually connected in a fashion that makes it a one-way drain, that is so that things can only go in one direction through the drain. The thoracic cavity has very special mechanical dynamics in the course of normal resting respiration or under the special circumstance of positive pressure ventilation.

In normal respiration the intrathoracic pressure is entirely negative throughout the entire cycle of respiration. Exceptions are the alterations that occur with a Valsalva maneuver, a sudden violent cough or a sneeze. If an abnormal opening is made between the thoracic cavity and the outside atmosphere, the pressure within the thoracic cavity quickly equalizes with the atmosphere, the lung collapses and there is a pneumothorax. If we place a one-way valve in the abnormal opening, this allows passage of material out of the intrathoracic cavity to the outside but not into it. This would permit no further collapse of the lung, but would not very efficiently reexpand the lung under resting, negative pressure conditions, unless we had a very cooperative patient who could do positive pressure maneuvers, such as coughing or sneezing. This works very well for the average 25-year-old person, with a spontaneous pneumothorax, but it does not work very well for a small baby.

The most frequent cause of problems that lead to the placing of chest tubes on a pediatric service is positive pressure ventilation. In this situation the intrathoracic pressure is continuously positive. If an abnormal opening were made between the outside and the intrathoracic cavity, nothing much would happen because the intrathoracic pressure is greater than atmospheric pressure. On the other hand, if an abnormal opening were made in the lung, very quickly air under positive pressure would be pumped into the thoracic cavity and a tension pneumothorax would result. To repair that tension pneumothorax with a chest tube there is no great need for negative pressure or one-way valves or anything of that sort because air would be quickly expelled by the positive pressure of the ventilator or continuous positive airway pressure.

Some attention should be devoted to what is necessary to put in a chest tube. I favor the trochar-type chest tube but a variety of instruments available are quite satisfactory. It is im-

portant also to have available such things as a simple needle or a butterfly-type needle or an Intracath® for the quick emergency treatment of a sudden pneumothorax, especially if the child is on a ventilator. It is important to remember that with any child who is on a positive pressure ventilation system who has been quite stable and suddenly turns sour, a pneumothorax is likely. The child with a tension pneumothorax usually on a ventilator, turns sour and becomes cyanotic. Time may be lost with head scratching or the taking of x-ray films but one may simply put a needle in the chest and save the child's life. Later one could at leisure place the chest tube. Initial aspiration of a pneumothorax can be done very easily with a needle and syringe. Butterfly needles are more convenient for one can make a water-seal drainage system by placing the butterfly needle into the chest and the little tubing of the butterfly into a cup of water.

A chest tube is usually connected to a drainage system and this is a place where confusion is common. The simplest chest drainage is the water-seal system. There are some important features. One is that it has to be open to the atmosphere for the system to operate properly. No suction is applied to the system, and it depends on positive intrathoracic pressure being developed by the patient by coughing or a ventilator for the evacuation of the abnormal substance in the chest. In the water-seal system the little tube is 2 cm below the level of the water. This means that at least 2 cm of positive pressure has to be developed in the child's chest before any flow can occur from patient to bottle. This is something we often forget. If there is blood or pus as drainage occurs the level in the water seal rises and the system changes. If the level which starts out at 2 cm reaches 10 cm, a new pneumothorax can develop.

The position of a chest tube is important. For a pneumothorax the tube should be in the apex of the chest. I prefer to put them through the midaxillary line but the anterior chest wall is also reasonable. It is important after a chest tube is placed that one immediately has an x-ray study made to be sure that the tube has done its job. In the case of a pneumothorax, the job is done instantaneously. As soon as it is placed and connected, that is the end of the pneumothorax if it has been done properly. Chest tubes have a way of getting into subcutaneous tissue elsewhere. An immediate x-ray film of the chest, looked at by the person who put the chest tube in, is mandatory. I furthermore feel that in every patient in whom a chest tube has been placed an x-ray film of the chest should be done every day thereafter to make sure that the tube is doing what it is supposed to do.

The standard, three-bottle suction system provides three bottles to do three different jobs. The first bottle, the collection bottle, is connected directly to the patient and obviates the problem of drainage collecting in the water seal bottle, so that the pressure in that bottle will not build up with increased drainage. The next bottle is the pressure-regulator bottle which is the one that determines how much suction is applied to the child's chest. This is determined by the placement of a tube beneath the level of the water. The last bottle of the series is the water seal bottle. This system is different from the water-seal system in that it is a closed system. The last tube goes to the wall suction. Because it is a closed system, it must be turned on. If one turns off the suction machine, it becomes a closed system, or essentially a clamped chest tube with no place for anything to go. So if one is going to disconnect this system one should disconnect the tubing from the wall suction and leave it open to the air converting a suction system to a water-seal system. The suction should *never* be turned off and left connected. Furthermore, in the way the bottles are connected the pressure regulator bottle is continuously bubbling, and since the water seal bottle is distal to it, the water seal bottle will also be continuously bubbling. This does not mean that there is a leak in the patient or a leak in the tubing. In this system vacuum source of minus-1,000 cm of water is reduced by the pressure regulator bottle to minus-15.

Another system is called a Pleurovac.® It differs in the positions of the pressure regulator and water seal bottles which have been reversed. Again, the minus-1,000 or whatever that comes from the wall is immediately dropped by the pressure regulator so that the next tubing down the line has minus-15 cm of water pressure. However, there are 2 cm of positive pressure that must be overcome by anything exiting from the chest to get into the water seal, reducing effective suction by another 2 cm.

Another thing that is sometimes confusing is how fast the bubbles should be bubbling. The rapidity of bubbling has nothing to do with the amount of suction applied to the child's chest. That is determined by the pressure regulator,

usually at 15 cm of water. The rate of bubbling has to do with the flow rate. That becomes important only when one has a major air leak. For example, in a medium-sized child on a ventilator who has a tidal volume of 200 ml at a rate of 20 breaths per minute and is leaking 50 ml into his thorax at every breath, one liter of air will be leaked each minute into his thoracic cavity. Obviously if we are not sucking out one liter of air per minute the pneumothorax will persist. In most situations there is no continuous air leak and the lung is reexpanded instantaneously when the tube is placed. In children who are on ventilators and have a continuous air leak, this becomes crucial. In general, the rate of bubbling cannot be too fast. In a postoperative cardiac patient where the chest tube is placed primarily for the drainage of blood, a slow rate of bubbling is perfectly reasonable but when one is worried about an air leak, a fast rate of bubbling is important. It must exceed the rate of the leak.

For some reason it is written in nursing manuals, and most people are taught, that if anything goes wrong with a chest tube a clamp should be placed on it. There is usually a little bundle of clamps at the foot of the bed or around the chest tube for just this purpose. The most important thing I can accomplish in this discussion is to get one message across: never clamp a chest tube. The reason is that if you clamp a chest tube and a continuous air leak persists, a tension pneumothorax will develop very quickly. This usually happens when the patient goes to the x-ray department or is being transported from one room to another and someone puts a clamp on the chest tube. About the time the patient reaches the elevator he gets a tension pneumothorax. A patient can quickly die under these circumstances. If the patient must be moved some place, merely disconnect the system from the wall suction and leave it open to the atmosphere: do not clamp it there either.

The management of empyema is illustrated by the case of a 5-year-old youngster whose situation was not dissimilar to the one we saw in the case presentation. The history was also similar. An upper respiratory infection suddenly became acutely much worse and high fever developed. The classic air-fluid levels were seen in the chest film. This was drained using a chest tube. The organism was the staphylococcus.

The treatment of empyema, in addition to medical therapy, should in all cases involve drainage as provided by an indwelling chest tube. Long-term drainage in children with staphylococcal pneumonia is not that long-term. The organisms are sensitive to antibiotics and with drainage the problem will resolve relatively rapidly. But for most children, long-term means a week to ten days. In the treatment of empyema we tend to place the tube posterior and low in order to put the chest tube in the empyema.

The removal of chest tubes has often been shrouded in mystery and mystique but it is very simple. One can cause a pneumothorax at the time of removing a chest tube. I simply place a petroleum jelly (Vaseline®) gauze pledget over the exit site and with one swift pull remove the tube. Appropriate bandages are placed and an x-ray film of the chest is obtained to make sure that there is no pneumothorax.

Pneumatoceles are seen in children with staphylococcal pneumonia usually in convalescence. We may see infants present with pneumatoceles, having completely missed the pneumonic phase of their disease. Virtually all pneumatoceles will completely resolve assuming the infection has been successfully treated and the empyema drained.

Dr. Goscienski: The prognosis of staphylococcal pneumonia has improved considerably in the past quarter century. Ceruti[6] studied 36 children from two to four years after their episodes of staphylococcal pneumonia and found that the radiologic features, results of pulmonary function testing at rest and after exercise, the incidence of respiratory infections in later years and rate of growth were all normal with only one exception. Therefore, the issue in staphylococcal pneumonia is the proper management of the initial life-threatening illness. If the patient survives this, the prognosis is good.

Dr. Nyhan: *Thank you very much. Are there questions?*

Question from the audience: *If you suspect staphylococcal pneumonia in an outpatient who is not severely ill, do you use oxacillin?*

Dr. Goscienski: We feel that any child less than 6 months of age who has what appears to be bacterial pneumonia should be treated with an antistaphylococcal agent, but I would never treat such an infant as an outpatient. If you are concerned about staphylococcal disease to the point where you would consider using dicloxacil-

lin, then the child belongs where he can be observed very carefully, because of the dramatic changes that can occur in staphylococcal disease. I would like Dr. Nyhan to comment on that, because he has had a great deal of experience with staphylococcal pneumonia.

DR. NYHAN: I would just echo what Dr. Goscienski said. The other comment I would make about the ambulatory treatment of children with pneumonia is that most of the children with pneumonia who can be sent home are those with a patchy bronchopneumonic process. If you see a lobar consolidation, even in a 6-year-old child, that has different implications, and most of those patients should come into the hospital.

QUESTION FROM THE AUDIENCE: *What is the risk of fistula formation?*

DR. CANTY: From a chest tube? Almost zero. Chest tubes do not cause infection. They are there to drain infection. A bronchopleural fistula is characterized by a huge air leak, that has to be taken care of by a high flow, high suction, big bore chest tube.

QUESTION FROM THE AUDIENCE: *What about decortication procedures?*

DR. CANTY: The long-term prognosis for a child who has had a staphylococcal pneumonia is as Dr. Goscienski pointed out, excellent. The so-called fibrothorax is a holdover from old-time thoracic surgery in people who have had tuberculous or Klebsiella empyemas. Fibrothorax and restrictive lung disease just do not occur in children. Even though there is some minimal pleural thickening, one does not have to go back and remove a peel in children. The complication just does not happen in children.

QUESTION FROM THE AUDIENCE: *We have been told to clamp a chest tube in order to see if it is ready to be discontinued.*

DR. CANTY: If you think about that for a minute, it makes absolutely no sense. What it proposes is a stress test; that is, let us see if he really needs this chest tube. Well, if he really needs this chest tube that means there is a continuous air leak but you can tell this by looking at the water seal bottle. If there is a leak then you should not clamp the chest tube. On the other hand, if there is no leak from the water seal bottle, pulling the chest tube is the appropriate response.

DR. NYHAN: *In conclusion we have considered the clinical features of acute staphylococcal pneumonia and reviewed the roentgenographic findings. Medical therapy is based on the use of a penicillinase resistant penicillin, most commonly oxacillin, delivered intravenously at least for the first few weeks. Staphylococcal pneumonia is characterized by the presence of empyema or pyopneumothorax. Chest tube drainage is mandatory.*

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Refer to: Paget disease of bone—Medical Staff Conference, University of California, San Francisco. West J Med 129: 210-224, Sep 1978

Paget Disease of Bone

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and Robert C. Siegel, Associate Professor of Medicine and Orthopaedic Surgery, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *It has been our custom each year to ask the chief medical residents to present one Medical Grand Rounds on a topic of their choice during the course of the year. Dr. Steven Harris is planning a career in endocrinology following the completion of his residency in medicine. His topic is one of long-standing interest to those concerned with metabolic bone diseases, that of Paget† disease of bone. Paradoxically, as he will note, there is little evidence that Paget disease is either metabolic or endocrine in origin. Nevertheless it is an important disorder of diverse clinical manifestations. Furthermore, there are new approaches toward therapy which are worthy of current review.*

DR. HARRIS:‡ On November 14, 1876, Sir James Paget, speaking before the Royal Medical and Chirurgical Society of London, presented a clinical description of a patient whose case he had followed for 20 years. Included in his presentation were notes on four similar cases with which he was familiar. It is quite likely that earlier authors had described the same disease process. In 1867, Wrany had noted findings in a 50-year-old woman who had died with what he termed "spongy hyperostosis" of the skull, pelvis, femur and vertebral column. Wilks introduced the term "osteoporosis, or spongy hypertrophy of the bones" in 1869,[1] while Czerny, writing in the Austrian literature, employed the term "osteitis deformans" to characterize a "rare acute inflammation of the lower part of the tibia and fibula inducing softening and angular bending and followed by hardening."[2] Paget also used the term "osteitis deformans" to describe his patient, using the name because of the conviction that the primary disease process was an inflammation of bone; he did suggest at the time, however, that "a better name may be given when more is known of it."[3] A lack of pathophysiologic revelation over the course of the past century is reflected in the fact that the disease is still known as osteitis deformans, or more familiarly as Paget disease of bone.

There is evidence that Paget disease has existed since antiquity. In fact, Sir Henry Trentham Butlin, the pathologist who worked with Paget, is said to have felt that the skull of the original Neanderthal man exhibited features of Paget disease.[4] Nevertheless, it is fitting that osteitis deformans should continue to be associated with the eponym Paget disease because Paget's description of the course of the disease, culled from 20 years of observation before his patient's death, is remarkable in its clarity. In describing his patient, Paget wrote as follows: "The short narrow chest suddenly widened into a much shorter and broad abdomen, and the pelvis was wide and low. The arms appeared unnaturally long, and, though the shoulders were very high, the hands hung low down by the thighs and in front of them. Altogether, the attitude in standing looked simian, strangely in contrast with the large head and handsome features."[3]

In summarizing the course of the disease, Paget noted that, "It begins in middle age or later, is very slow in progress, may continue for many years without influence on the general health, and may give no other trouble than those which are

*Lloyd H. Smith, Jr. MD, Professor and Chairman, Department of Medicine.

†The WESTERN JOURNAL's style regarding eponyms is that they are not written in the possessive form; therefore, Graves disease, Ewing sarcoma and Paget disease. An explanation may be found on page 78 of the July 1978 issue.

‡Steven Harris, MD, Chief Medical Resident.

due to the changes of shape, size, and direction of the diseased bones. Even when the skull is hugely thickened, and all its bones exceedingly altered in structure, the mind remains unaffected. The disease affects most frequently the long bones of the lower extremities and the skull, and is usually symmetrical. The bones enlarge and soften, and those bearing weight yield and become unnaturally curved and misshapen. The spine, whether by yielding to the weight of the overgrown skull, or by change in its own structures, may sink and seem to shorten with greatly increased dorsal and lumbar curves; the pelvis may become wide; the necks of the femora may become nearly horizontal, but the limbs, however misshapen, remain strong and fit to support the trunk. In its earlier periods, and sometimes through all its course, the disease is attended with pains in the affected bones, pains widely various in severity and variously described as rheumatic, gouty, or neuralgic. . . ."[3]

Prevalence

Paget disease in its symptomatic form, with bone pain and deformity, constitutes one end of the spectrum of the disease. A more limited form of the disease may remain clinically silent, therefore the prevalence of Paget disease remains somewhat uncertain. In 1932, reporting on the results of 4,614 necropsies on unselected persons in Dresden over the age of 40 years, Schmorl noted a prevalence of Paget disease of 3 percent.[5] Collins recorded a similar prevalence of 3.7 percent in an autopsy series of 650 patients over the age of 40 years at two general hospitals in Yorkshire; of note is that the diagnosis of Paget disease had been made antemortem in only 29 percent of the cases.[6] In a British radiologic series, Pygott found 357 cases of Paget disease in a five-year period. From estimates of the number of persons in each age group undergoing radiographic examination during that same period, estimates of the prevalence of Paget disease were derived.[7] The prevalence of Paget disease was found to be 3.5 percent among patients over the age of 45 years, a figure similar to that derived from the two earlier autopsy series, but the prevalence was estimated to be as high as 11 percent in one subset of the population, women over the age of 85 years. Given these prevalence estimates, Barry feels that Paget disease may be second in frequency only to osteoporosis among the bone diseases studied to date in occidental populations.[8]

Symptomatology

Krane has suggested that symptoms in Paget disease may arise from bone pain, deformity or fracture of involved bone, change in the temperature of skin overlying involved bone, compression of neural structures, alteration of joint structure and function, and as a consequence of increased vascularity or shunting.[9] Symptoms present at the time of initial presentation have been summarized in Table 1; the summary is by no means all-inclusive, but presents data from four investigators at different institutions. Although a variety of initial symptoms was noted, bone pain was the most common presenting complaint in all four series.

Sites of Involvement

The studies of initial symptomatology have been complemented by analyses of the frequency with which various bones have been involved by the pagetic process. The analyses, represented by those studies listed in Table 2, have all had obvious shortcomings. The autopsy studies by Schmorl and Collins did not examine every bone of the body in detail, while the radiologic studies by Frank, Gutman, Dickson and Rosenkrantz included findings in selected populations of patients examined with a largely-unspecified degree of roentgenographic thoroughness. The single scan study by Shirazi, like the earlier radiographic studies, presented findings in a selected patient population at a particular time. Given the above reservations, it nevertheless appears that the axial skeleton is involved most frequently, the lower extremities are involved more frequently than are the upper extremities, the lumbosacral spine is affected more often than is the balance of the vertebral column and the tibia is involved more frequently than is the fibula.

Histology

In 1974 Rasmussen and Bordier proposed a model for the cellular events occurring on the endosteal surface of normal bone. In brief, osteoprogenitor cells were posited to give rise to a population of multinucleated osteoclasts responsible for the resorption of pre-existing bone. Osteoclasts in turn were felt to undergo fission, yielding mononuclear osteoblasts, cells devoted to the laying down of the collagenous matrix of new bone. Osteoblasts becoming surrounded by newly-mineralized matrix were termed osteocytes, and were felt to be capable of participation in

both bone resorption—so-called osteocytic osteolysis—and bone formation.[16]

Histologically, the initial event in Paget disease seems to be a pronounced increase in bone resorption by osteoclasts and perhaps osteocytes.[16] In 1944 Reifenstein and Albright took biopsy specimens from a circumscribed area of bone destruction in the skull of a patient with Paget disease, showing the presence of osteoclasts without osteoblasts at the junction of normal and involved bone.[17] The osteoclasts show notable variability both in size and in number of nuclei; more than 100 nuclei may be present in a single osteoclast. This morphologic heterogeneity is said to be present only in Paget disease.[16] The initial osteolytic phase of the disease is generally followed by a mixed phase characterized by a compensatory increase in osteoblastic activity.[9] The

TABLE 1.—*Symptoms Present at Time of Presentation*

Symptoms at time of presentation	*Kay(1934)[10] 34 cases (Percent)*	*Gutman(1936)[11] 116 cases (Percent)*	*Dickson(1945)[12] 367 cases (Percent)*	*Rosenkrantz(1952)[13] 111 cases (Percent)*
Bone pain	..	54	..	50
Lower extremities	29	..	36	..
Back	6	..	32	..
Hips	..	..	15	..
Headache	6	27	17	13
Fracture of bone	12	14	..	..
Bone deformity	12	41	..	..
Gait disturbance	6	33	..	7
Skull enlargement	..	24	..	9
Deafness/vertigo/tinnitus	..	22/19/..	14/10/ 7	13/ 7/..
Paresthesias/neuralgia	..	5/..	../ 5	..
Fatigue	..	..	13	..
Urinary symptoms including calculi	..	..	..	13
Asymptomatic	18	19	20	..

TABLE 2.—*Sites of Involvement*

Site	*Schmorl[5] (1932) 4,614 pt (Percent)*	*Collins[6] (1956) 46 pt (Percent)*	*Franck[14] (1974) 55 pt (Percent)*	*Gutman[11] (1936) 116 pt (Percent)*	*Dickson[12] (1945) 367 pt (Percent)*	*Rosenkrantz[13] (1952) 111 pt (Percent)*	*Shirazi[15] (1974) 100 pt (Percent)*
Skull	28	65	55	78	42	42	48
Spine	50	..	..	..	..	..	63
Cervical	..	..	9	11	2	6	8
Thoracic	..	..	27	41	14	2	34
Lumbosacral	..	76	42	55	28	39	LU 40
	S 56	..	..	..	..	..	S 28
Pelvis	22	43	L 66	90	66	63	78
	..	..	R 58	..	..	..	..
Femur	R 31	35	96	65	47	R 41	R 34
	L 15	..	..	..	..	L 34	L 34
Tibia	8	30	44	54	35	R 9	R 18
	..	..	..	..	..	L 11	L 13
Fibula	..	4	18	6	2	R 3	2
	..	..	..	..	..	L 3	..
Humerus	4	..	40	59	5	R 9	R 16
	..	..	..	..	..	L 8	L 6
Clavicle	13	11	18	24	9	R 3	3
	..	..	..	..	..	L 5	..
Sternum	23	7	2	..	..	..	4
Scapula	..	..	20	29	2	R 3	37
	..	..	..	..	..	L 5	..
Radius	..	..	11	26	2	..	..
Ulna	..	..	7	19	1	..	..
Ribs	..	2	13	13	3	4	5
Hand phalanx	..	..	27	..	..	..	..
Metacarpal	..	..	13	..	..	..	..
Tarsal/Metatarsal	..	..	9/ 9	..	..	..	..
Patella	..	..	5	2	1	..	..
Maxilla	..	..	4	..	..	..	..
Mandible	..	..	4	..	..	1	4
Facial bones	..	..	..	..	..	..	2

L = left R = right S = sacral LU = lumbar

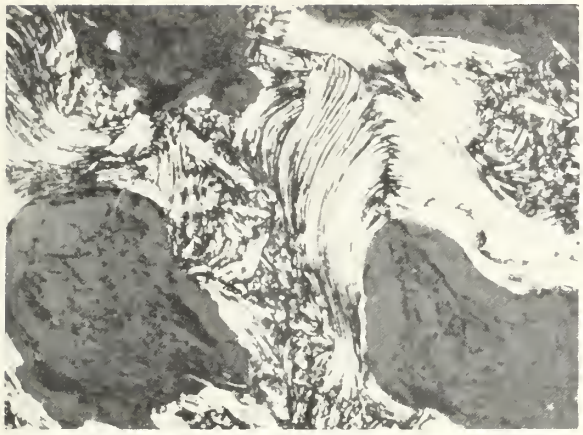

Figure 1.—Lamellar bone interspersed with woven bone. The woven bone is distinguished by a lack of parallel collagen fibers. Decalcified, polarized. (Reproduced by permission of the publisher from Singer FR[18]).

Figure 2.—Lateral radiograph of skull involved with the mixed phase of Paget disease (Provided through the courtesy of Dr. Harry Genant).

osteoblasts, which have abnormal structural heterogeneity as do the osteoclasts, lay down primitive woven bone, which is ordinarily not found in adults, as well as structurally abnormal lamellar bone, as illustrated in Figure 1. The lamellar bone, which is characteristically deposited in a mosaic pattern, nevertheless appears to undergo mineralization normally in most cases.[18] In this active phase of the disease the normal hematopoietic bone marrow is replaced by loose, fibrous connective tissue and characteristic large vascular channels.[18] With time, osteoclastic activity may decrease, and the disease enters a sclerotic or osteoblastic phase.[9] In this stage, the bone marrow abnormalities may revert to normal.[18]

In normal bone, accretion of new bone on the periosteal surface may occur without a preceding resorptive process.[16] Normally with aging, however, net resorption on the endosteal surface exceeds periosteal accretion so that the transverse diameter of bone increases with time, but cortical thickness decreases. In Paget disease, however, net accretion of bone may occur on both the periosteal and endosteal surface, leading to an increase in both the transverse diameter and cortical thickness of bone.[16] During the mixed and sclerotic phases of the disease, as seen radiographically in Figure 2, accretion of bone on the periosteal surface of the skull may lead to an increase in the external dimensions,[19] therefore the circumference of the hat of Paget's original patient increased from 22½ inches to 27¼ inches over the course of 22 years.[3] Some accretion of bone may occur on the dural surface of the skull as well, but it is unusual for symptoms to arise from frank compression of the cerebral hemispheres.[19]

Radiologic and Scintigraphic Findings

The microscopic changes in Paget disease are reflected in macroscopic alterations in bone structure detectable on roentgenographic examination. The characteristic radiologic findings have been well-summarized in the past,[19] and will not be presented in detail here. When the osteolytic phase of the disease involves the skull, as shown in Figure 3, it is termed osteoporosis circumscripta; it usually begins in the frontal or occipital areas, and may spread to involve the entire calvarium.[19] Pagetic involvement of a long bone is usually initially manifest radiographically as a V-shaped resorption front beginning at one end of the bone.[20] Figure 4 shows advanced, sclerotic involvement of the tibia, with sparing of the fibula. Incomplete fractures, also termed fissure fractures, may occur at areas of tension, characteristically on the convex border of the bone.[19] Paget disease may produce enlargement of the body of a single involved vertebra,[21] while involvement of the pelvis may be differentiated from metastatic prostatic carcinoma by the presence of the so-called brim sign, a thickening of the pelvic brim. In one series, the brim sign was present in 85 percent of cases of generalized pagetic involvement of the pelvis, while present in only one of 250 cases of carcinoma metastatic to the pelvis.[22]

Bone scans employing a variety of radiotracers, including ^{85}Sr, ^{87m}Sr, ^{18}F, and ^{99}Tc-labeled phosphates, have also proven useful in the evaluation of the extent of the pagetic process. When the disease involves multiple bones—so-called poly-

ostotic Paget disease—the pattern of involvement on bone scan is said to be quite characteristic. When only a single bone is involved, in the monostotic form of the disease, the differentiation of Paget disease from other processes such as fracture, infection or metastatic disease may be more difficult.[15]

Several authors have attempted comparison of the sensitivity of bone scan and x-ray studies in the detection of bony involvement by Paget disease. The data in Table 3 suggest that bone scan and radiographic examination are complementary in the detection of sites of involvement. Lesions detected by x-ray studies alone tended to be in the sclerotic phase of the disease,[15,23,26] while lesions visualized on scan alone were speculated to be in the early osteolytic phase.[26] Those lesions seen on scan alone tended to be symptomatic, while the sclerotic lesions shown on x-ray films alone tended to represent an asymptomatic burned-out phase of the disease.[23]

Complications

As suggested by Table 1, which details presenting symptomatology in cases of Paget disease, the basic alteration in bone structure may lead to a variety of local and systemic complications. The most common complication appears to be bone pain, although the cause of the pain remains uncertain.[18]

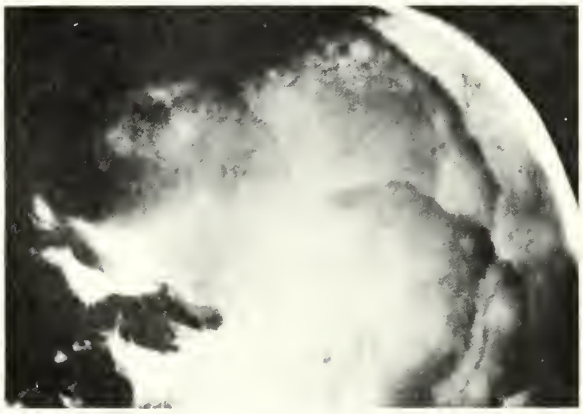

Figure 3.—Lateral radiograph of skull showing osteoporosis circumscripta (Provided through the courtesy of Dr. Harry Genant).

Deformity of involved bones is a major complication as well. In the lower extremities, the force of weight-bearing tends to be transmitted as tension on the lateral surface of the femur and compression on the medial surface. A tendency toward bone accretion on the lateral side, subjected to tensile forces, with resorption on the compressed medial side, leads to progressive lateral bowing of the weakened femur affected by Paget disease.[27] This type of deformity alters the mechanical stresses to which neighboring joints are subjected, predisposing to degenerative arthritic changes.[28] In addition to degenerative arthritis, Paget disease has been linked with calcific periarthritis, gouty arthritis and with a syndrome similar to ankylosing spondylitis,[14] but the strength of these associations remains to be confirmed.

The weakened structure of pagetic bone may lead not only to deformity but also to fracture,

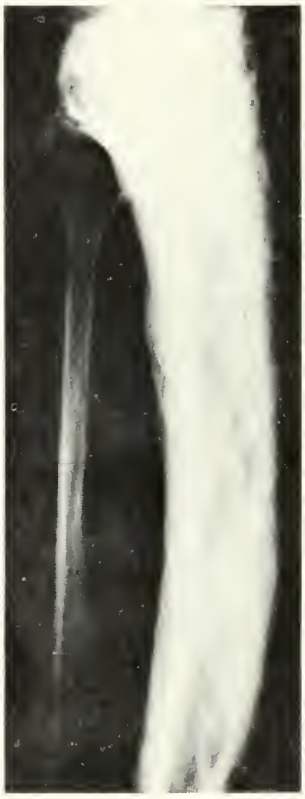

Figure 4.—Deformed tibia exhibiting largely sclerotic phase of Paget disease; fibula is spared (Provided through the courtesy of Dr. Harry Genant).

TABLE 3.—*Comparison of Radiographic and Scintigraphic Detection of Sites of Involvement*

	Khairi(1973)[23]	*Lentle(1976)*[24]	*Lavender(1977)*[25]	*Wellman(1977)*[26]	
Time of evaluation	..	..	..	<1 yr after dx	>1 yr after dx
Number of patients	22	15	8	39	57
Total Number of lesions	92	137	80	112	204
Lesions detected by x-ray & scan	64(70%)	99(72%)	69(86%)	65(58%)	123(60%)
Lesions shown by x-ray alone	13(14%)	3(2%)	9(11%)	11(10%)	31(15%)
Lesions shown by scan alone	15(16%)	35(26%)	2(3%)	36(32%)	50(25%)

with pathologic fractures tending to involve the femur and tibia.[18] Complete fractures of long bone tend to involve the femur most commonly, frequently occurring as transverse chalk-stick fractures through the shaft just below the lesser trochanter.[8,18] The occurrence of incomplete fissure fractures on the convex borders of bone has already been mentioned. Compression fractures of involved vertebrae may be noted as well, with more frequent involvement of the lumbar and thoracic vertebrae than cervical vertebrae.[12]

Hearing loss has been estimated to be present in 30 percent to 50 percent of patients with skull involvement, while vestibular dysfunction is present in 20 percent to 25 percent.[29] The hearing loss is most often mixed in nature, with both sensorineural and conductive deficits.[29] Changes in the architecture of the temporal bone in the region of the petrous pyramid may cause cochlear dysfunction responsible for the sensorineural loss. The conductive deficit may arise from a variety of processes including ankylosis of the footplate of the stapes, impaired mobility of the ossicular chain, occlusion of the external auditory canal and narrowing of the eustachian tube, leading to chronic otitis media.[30] Limited information about abnormal physiognomy and pronounced thickening of the cranial vault at postmortem examination have led to speculation that Beethoven's deafness was attributable to involvement of his skull with Paget disease.[31]

A variety of osseous neoplasms have also been recognized as complications of Paget disease; they have been classified as osteosarcomas, chondrosarcomas, fibrosarcomas, and benign and malignant giant cell tumors.[32] The bones most commonly affected by sarcomatous degeneration are the femur, humerus, skull, pelvis and tibia;[18,33] giant cell tumors tend to develop in the skull and facial bones.[8] The humerus is involved with sarcoma more often than might be expected from the frequency of its involvement with the pagetic process, while the spine is involved with malignant change much less often than predicted.[18,33] In Milgram's experience at the Armed Forces Institute of Pathology, bone adjacent to an area of sarcomatous degeneration shows very active Paget disease. This has led to speculation that the risk of malignant change in any given bone decreases as the activity of the pagetic process in that bone wanes.[34] Despite the fact that in three of Paget's original five patients osseous neoplasms developed,[3] sarcoma has been estimated to develop in only 0.9 percent to 2 percent of larger series of patients. In patients with polyostotic disease, however, sarcoma has been reported to arise with a frequency of 7 percent to 22 percent. Presenting symptoms of sarcoma have most commonly included localized pain, rapid swelling or pathologic fracture.[32] Historically, the sarcomas have been notoriously resistant to therapy,[32] with only transient palliation from radiotherapy,[8] although combination chemotherapy has yet to be applied to a series of patients with sarcoma complicating Paget disease.

A variety of neurologic signs and symptoms has been reported as sequelae of Paget disease. Schmidek has suggested that neurologic changes may arise by several mechanisms, such as pressure exerted by pathologic bone along the neuraxis, changes in the weight-bearing ability of bone, local invasion by areas of neoplastic degeneration and vascular insufficiency of neural structures.[35] Compressive phenomena may result in cranial nerve dysfunction, including trigeminal neuralgia and its seventh nerve motor equivalent, hemifacial spasm.[36] Weakening of bone at the base of the skull permits the skull to sag on the vertebrae, a condition termed platybasia. The odontoid process projects through the foramen magnum, producing pressure at the cervicomedullary junction as well as compression of posterior fossa structures; obstructive hydrocephalus as well as brain stem and cerebellar dysfunction may result.[35] Pagetic involvement of the vertebral column may result in spinal cord compression by bony overgrowth, fracture, or dislocation. Involvement of the thoracic spine most often produces symptoms, for the vertebral canal is narrowest in that region. Spinal involvement may also produce nerve root compression by encroachment on intervertebral foramina.[37]

High-output congestive heart failure is a well-recognized complication of Paget disease. Functional arteriovenous communications have been implicated by hemodynamic studies on patients with the high-output state which show tachycardia, widened pulse pressure, low systemic vascular resistance and elevated venous oxygen content.[38,39] However, anatomic communications have never been successfully shown by arteriography, injection of Tc-labeled microspheres, or direct histologic examination.[39,40] In a quantitative radiographic study, Howarth found the high-output state to be present only in patients with greater than 35 percent skeletal involvement with

the pagetic process.[41] Cardiac output has also been shown to correlate with biochemical indices of the activity of the Paget disease.[42]

In 1945 Edholm described the case of a 66-year-old man with polyostotic disease and clinical evidence of biventricular congestive failure who had a measured cardiac output of 13.3 liters per minute. Blood flow to the affected bone was estimated by crude plethysmographic methods to be 20 times normal; temporary occlusion of arterial flow to the affected limb with a cuff led to improvement in the hemodynamic measures of the high-output state.[43] Wootton and associates measured skeletal blood flow in 24 patients with untreated Paget disease utilizing radionuclide tracers; they found that skeletal blood flow per minute constituted 4.4 percent to 18.9 percent of the total blood volume in the pagetic patients as opposed to 4.4 percent to 5.9 percent in eight normal volunteers.[44,45] Regional blood flow has also been assessed by application of an electromagnetic flowmeter to the exposed carotid bifurcation before and after ligation of the external carotid artery in two pagetic patients with sarcomatous degeneration of involved skull. Flow through the external carotid system was found to be much greater than normal.[46] It has been speculated that notably increased flow through the external carotid artery in patients with severe pagetic skull involvement may shunt blood away from the brain—a so-called pagetic steal syndrome. The presence of increased external carotid flow may be suggested clinically by an increase in the size of the superficial temporal artery.[18]

In 1909 Klippel and Weil reported that the surface temperature of a pagetic limb may be as much as 5°C warmer than that of the corresponding uninvolved limb.[47] Heistad utilized that observation in studies on three patients with Paget disease involving only one extremity. Using plethysmographic methods, resting blood flow in the pagetic extremity was found to be approximately six times the flow in the contralateral normal extremity. With epinephrine iontophoresis to suppress blood flow to the skin but not to the underlying tissue, flow to the pagetic extremity was reduced close to the normal range. Local heating, which increased cutaneous blood flow only, produced a larger increment in flow to the normal extremity than to the pagetic limb. Blood flow to the heated normal limb was comparable to flow to the resting pagetic limb. From these observations, Heistad concluded that dilatation of the normal cutaneous vascular bed could explain the increased blood flow seen in pagetic extremities.[48]

In addition to the complications noted above, a variety of other disease processes have been linked to Paget disease. It has been claimed that valvular and arterial calcification occur with increased frequency in pagetic patients, as may calcification of the interventricular septum with complete heart block.[49] Associations with diabetes mellitus, Hashimoto thyroiditis, pseudoxanthoma elasticum and a folate-dependent malabsorption syndrome have also been claimed.[50-52] The significance of these observations remains uncertain.

Biochemical Measures

Calcium kinetics studies utilizing the radiotracer ^{47}Ca have suggested that the bone resorption and formation rates in active Paget disease may be increased up to 20 times normal. It has been speculated that the increased bone formation rate may teleologically represent an attempt to maintain calcium homeostasis in the face of notably increased influx of calcium from bone into extracellular fluid.[4] The fine balance in bone formation and resorption rates is reflected biochemically in the fact that serum calcium, phosphorus and parathyroid hormone levels are usually normal; urinary calcium is most often normal as well.[4,9] Immobilization of the pagetic patient, however, may upset the balance. In 1944 Reifenstein and Albright reported two cases of hypercalcemia occurring in pagetic patients immobilized after sustaining fractures. It was felt that the immobilization led to a decrease in bone formation rate while bone resorption continued unabated. The consequent hypercalcemia posed a threat of causing what was termed a chemical death.[17] Gordan has argued that the threat of hypercalcemia in immobilized patients even with extensive Paget disease has probably been exaggerated. He has stated that in a series of 64 immobilized patients, the only patients in whom hypercalcemia was detected had coincident parathyroid adenomas.[53] Even if the incidence of frank hypercalcemia remains moot, hypercalciuria following immobilization seems to predispose to nephrolithiasis.[4,53]

Alkaline phosphatase, which has generally been used as an index of osteoblastic activity, was first found to be elevated to a pronounced degree in patients with Paget disease in 1929.[54] Woodard followed the cases of 36 untreated patients with serial alkaline phosphatase determinations over

a period of 5 to 21 years; the alkaline phosphatase tended to increase with time, but often showed fluctuation with a periodicity of months to years.[55]

Acid phosphatase levels, associated with osteoclastic activity, have been found to be elevated in a small number of patients with extensive Paget disease, but have not been widely used in following the course of the disease.[13,18,55,56] Osteoclastic activity, as reflected in bone resorption, has more conventionally been monitored utilizing urinary levels of hydroxyproline, a nonessential amino acid found in the body almost exclusively in collagen.[57] While the normal urinary excretion of hydroxyproline on a low-gelatin diet is less than 50 mg per 24 hours, daily excretion in Paget disease may be elevated to more than 2,000 mg.[18] Approximately 90 percent of urinary hydroxyproline is found in a so-called dialyzable fraction; this fraction consists largely of dipeptides and tripeptides felt to represent fragments of resorbed collagen.[9] The balance of urinary hydroxyproline is found in a nondialyzable fraction; radiotracer studies utilizing ^{14}C-L-proline have suggested that the peptides in this fraction have been derived either from collagen that has been synthesized and rapidly degraded, or from peptides that have been synthesized but not incorporated into intact tropocollagen at all.[58] Urinary hydroxylysine, like hydroxyproline, is derived largely from collagen degradation. Glycosides of hydroxylysine are present in different collagens in different ratios, therefore the pattern of glycoside excretion may give a more accurate indication of the type of collagen being degraded than does urinary excretion of hydroxyproline, which is found in all collagen in approximately the same proportion.[59]

Serum alkaline phosphatase and urinary hydroxyproline levels tend to be closely correlated. This suggests that bone formation and resorption are coupled. Both values tend to correlate with the extent of Paget disease as determined radiographically,[23] as well as with skeletal blood flow as measured by radiotracer techniques.[45] At times, however, biochemical changes may not parallel histologic changes on sequential bone biopsy studies;[16] such discrepancies must be interpreted in light of possible sampling error in biopsies.

Treatment

A variety of indications for the treatment of Paget disease have been suggested: bone pain, congestive heart failure, recurrent pathologic fractures, neurologic complications, and hypercalciuria or hypercalcemia. Prophylactic treatment for the prevention of bony deformity, and preoperative treatment to decrease bony vascularity before orthopedic procedures also have been suggested.[18,60,61]

Early therapies included use of potassium iodide,[3] arsenic,[2] staphylococcus vaccine, insulin, high-vitamin diets, parathyroidectomy and dihydrotachysterol;[13] none had consistent effect on the pathological process. Localized radiation therapy to affected bones was utilized with transient relief of bone pain.[11] Estrogen and androgen therapy was employed with relief of pain as well.[53] During the late 1940's and early 1950's, studies by Albright on the effects of adrenocorticotropic hormone (ACTH) and cortisone showed that corticosteroids in large doses, in the range of 500 mg to 1,000 mg of cortisone a day, could produce both biochemical and symptomatic improvement in pagetic patients.[62] Studies by Rapaport and associates using comparable doses of cortisone to treat six patients with the high-output state showed a fall in cardiac output ranging from 13 percent to 52 percent of baseline values.[38] Serial bone biopsy studies on cortisone therapy showed histologic improvement without definite anatomic obliteration of the abnormal vascular channels.[38,62,63] Unfortunately, cortisone in the dosages used appeared to produce an acute osteoporotic state with consequent vertebral collapse. Experience with cortisone therapy in smaller doses, on the order of 75 mg a day for three years, proved disappointing; no consistent change in biochemical or histologic measurements was noted.[63]

The experience with one anti-inflammatory agent, cortisone, prompted speculation that another anti-inflammatory agent, acetylsalicylic acid (ASA), might prove useful in the treatment of Paget disease. In a small number of patients, ASA in a dose of 4 grams to 6 grams a day was shown to produce an improvement in biochemical indices; calcium kinetics studies utilizing the radiotracer ^{47}Ca showed a decrease in bone turnover. In a single patient, skull biopsy after three weeks of ASA therapy showed histologic improvement.[64] Studies of salicylate levels, also on a single patient, suggested that a level of 25 mg per dl to 40 mg per dl was necessary for therapeutic effect; a decrease to 10 mg per dl was associated with relapse.[63] Although sustained clinical improvement has been reported in a small number of

patients treated with ASA for periods up to eight months,[64] positive biochemical and clinical results have not uniformly been found.[4]

During the 1960's, sodium fluoride was employed in the treatment of small series of pagetic patients. Doses of 60 mg to 120 mg of sodium fluoride a day were reported to provide biochemical improvement and pronounced symptomatic relief.[65-67] Once again, however, results were not uniformly reproducible.[4,68] Fluoride in toxic doses may produce so-called crippling fluorosis characterized by abnormal bone formation with cortical thickening, osteosclerosis, bone pain and multiple painful exostoses.[69] Concern over this potential toxicity has limited the use of fluoride in the treatment of Paget disease.

Trials of inorganic phosphate therapy have also been undertaken in small numbers of patients without consistent effect on alkaline phosphatase or hydroxyproline values.[24,70] Oral inorganic phosphate supplements in doses of 1 gram to 2 grams a day have been reported to produce amelioration of the high cardiac output state, although in some cases hemodynamic values subsequently returned to baseline levels in spite of continued therapy.[71,72] Relief of bone pain and associated symptoms has been reported to persist in spite of hemodynamic relapse.[72]

Over the past ten years there has been extensive use of the calcitonins, diphosphonates and cytotoxic agents in the treatment of Paget disease. The ability of thyrocalcitonin to inhibit parathyroid hormone (PTH)-induced bone resorption *in vitro* was established in the mid-1960's.[73] Since that time, the structures of the porcine, salmon and human forms of calcitonin have been identified, and all have been used in the treatment of Paget disease. On a weight basis, porcine calcitonin is the weakest form, while the salmon analogue is by far the most potent.[74] At this time only salmon calcitonin is readily available for clinical use, although synthetic human calcitonin is available on an experimental basis. All of the calcitonins must be administered parenterally.

Bone biopsy studies carried out in pagetic patients 30 minutes after the administration of an intravenous bolus of calcitonin have shown a decrease in the number of osteoclasts and an alteration in the ultrastructure of the remaining osteoclasts.[75] Histologic studies have been interpreted to show an inhibition of the activation of osteoprogenitor cells to osteoclasts, as well as an increase in the modulation of osteoclasts to osteoblasts. The immediate effect is a decrease in bone resorption and an associated transient increase in bone formation. As calcitonin therapy is continued, bone formation decreases as well, an indication of the decrease in the number of cells passing through the osteoprogenitor-osteoclast-osteoblast sequence.[16,76]

The observed histologic changes lead to a predictable sequence of biochemical changes in pagetic patients treated with calcitonin. Within hours of the administration of calcitonin, there is a transient, subclinical hypocalcemic response associated with an increase in circulating PTH and a decrease in urinary hydroxyproline excretion. The magnitude of the hypocalcemic response seems to be related to the prevailing rate of bone turnover at the time of treatment.[77-79] With sustained calcitonin therapy, a fall in alkaline phosphatase level is observed, suggesting the underlying decrease in osteoblastic activity.

The biochemical and clinical effectiveness of calcitonin in the treatment of Paget disease was first briefly reported in 1967.[80] Since that time, numerous studies, albeit uncontrolled studies, have documented the efficacy of treatment with porcine calcitonin,[70,74,81-84] salmon calcitonin,[74,82,85-88] and human calcitonin[89-91] for periods up to four years. The calcitonins have been administered in a wide variety of dosage regimens ranging from multiple divided daily doses[83] to single weekly injections of salmon[85] or human[89] calcitonin. In general, hydroxyproline and alkaline phosphatase both decrease approximately 30 percent to 70 percent during the first months of therapy before reaching plateau values. The plateau values are generally still well above the normal range, although frank normalization has been reported.[82] Bone biopsy specimens taken during biochemical remission may show the deposition of normal lamellar bone despite continuing therapy.[91] Symptomatic relief of bone pain attributable to direct pagetic involvement has been achieved in most treated patients. Functional improvement has been reported as well. Patients with elevated cardiac output may show improvement in hemodynamic variables with treatment,[42,72,92] although this has not been found consistently in all series.[93] Improvement in congestive heart failure may result in part from decreased skeletal blood flow[44] and in part from a natriuretic effect of calcitonin.[84,94] A variety of neurologic deficits along the neuraxis may decrease with therapy. As previously noted, spinal cord compression may

result from encroachment of abnormal bone; complete spinal block has been reported to resolve with protracted calcitonin therapy with virtually complete recovery of neurologic function.[82,95] Some patients with hearing deficits may show improvement in audiometric abnormalities with therapy, but subjective hearing improvement has unfortunately not occurred.[84,96,97]

Nausea, facial flushing and local dermatologic reactions have been seen with variable frequency and persistence during calcitonin therapy, but have not generally been severe enough to cause discontinuation of therapy.[74,82,90] Once therapy is stopped, biochemical remission may persist for six months to a year, with some indication that the length of remission is proportionate to the length of the treatment period.[90] Symptomatic remission may long outlast biochemical remission. In a series of patients treated with short, 18-day courses of porcine calcitonin, clinical remissions lasting from five months to almost four years were noted.[83]

During protracted calcitonin therapy, regression of radiographic abnormalities[89,98-100] and improvement in scintigraphic findings[25,101] have been reported in a small number of patients, but the changes are minimal compared with the magnitude of biochemical improvement.

As previously noted, biochemical values tend to plateau after several months of treatment with calcitonin. Frank rebound may occur, with a tendency for alkaline phosphatase and hydroxyproline to increase back toward baseline values despite continued calcitonin therapy. In one series, small chemical rebounds were noted in 35 percent of patients treated with porcine calcitonin and in 55 percent of patients treated with salmon calcitonin, despite sustained clinical improvement.[82] The causes of the plateau and rebound response remain obscure, although a variety of mechanisms have been suggested. In series of patients treated with porcine or salmon calcitonin for extended periods, calcitonin-binding antibodies were detected in 30 percent to 70 percent of patients.[82,102] There is some evidence that antibodies may appear most frequently in patients treated with relatively high doses of calcitonin for extended periods.[82] The antibodies are generally of the IgG class and do not bind human calcitonin *in vitro*. Calcitonin-binding antibodies have not been detected in patients who received treatment with human calcitonin alone.[90] There is no consistent correlation between antibody titer and biochemical rebound, although occasional cases of biochemical resistance apparently due to high-titer antibodies have been reported.[82,102,103] Such resistant patients may respond to subsequent therapy with human calcitonin.[103,104] Although antibody formation may explain some cases of rebound, at least half of the cases of rebound are not associated with detectable antibody.[82]

Secondary hyperparathyroidism as a consequence of calcitonin-induced hypocalcemia has also been invoked as a possible explanation for biochemical rebound. Dubé and associates described an increase in fasting PTH and disruption of the normal circadian rhythm of PTH secretion after 3 to 12 months of treatment with porcine calcitonin.[105] Burckhardt[106] and DeRose,[82] on the other hand, found normal baseline PTH levels, and normal PTH response to ethylenediaminotetraacetate (EDTA)-induced and calcitonin-induced hypocalcemia.

In two patients studied by Hamilton a rebound increase in hydroxyproline occurring during synthetic salmon calcitonin therapy was felt to be linked to phosphate depletion; orally given neutral phosphate was added to the calcitonin therapy with a subsequent decrease in hydroxyproline excretion.[87] Tentative *in vitro* evidence also exists that calcitonin therapy itself may produce a decrease in the number of calcitonin binding sites in bone.[107] However, none of the above proposed mechanisms—antibody formation, secondary hyperparathyroidism, phosphate depletion and down-regulation of calcitonin receptor sites—seems to have been conclusively established as sufficient explanation for the commonly observed plateau and rebound phenomenon.

During the past five years there has also been extensive experience with the use of diphosphonates in the treatment of Paget disease. The only diphosphonate studied widely to date has been disodium ethane 1-hydroxy-1,1-diphosphonate, also referred to as sodium etidronate or EHDP. The diphosphonates are orally-administered pyrophosphate analogues that are resistant to the action of endogenous pyrophosphatase. They have been shown to inhibit both bone resorption and formation, although the mechanisms involved remain somewhat unclear. The principal mode of action seems to be a physicochemical inhibition of both the formation and dissolution of hydroxyapatite crystals,[108] although direct effects on the metabolism of bone cells *in vitro* have been reported.[109] Biopsy studies of bone done in patients treated with EHDP have shown decreased numbers of

osteoclasts and osteoblasts.[110] Therefore, the diphosphonates, like calcitonin, may act to decrease the activation of osteoprogenitor cells.[111]

EHDP has been used in a variety of clinical trials up to 2½ years in length in doses ranging from 2.5 mg per kg of body weight per day to 20 mg per kg per day.[108,112-118] The biochemical and clinical results have been similar to those found with calcitonin, although no cases of biochemical rebound have been reported. An initial fall in hydroxyproline excretion is followed by a fall in alkaline phosphatase; both have decreased by 30 percent to 80 percent at the end of six months of therapy.[111,112,116] There is some evidence that the improvement in biochemical measures may be dose-related,[111,112,116] but DeVries found the differences to be a matter of rate rather than degree. In comparing doses of 7.5 mg per kg per day and 15 mg per kg per day, the smaller dose was found to produce the same biochemical improvement as the larger dose but in twice the time.[113] Pronounced symptomatic improvement occurring within the first several months of EHDP therapy has been reported in most patients studied. A significant placebo effect may confound the interpretation of subjective responses, however. In a controlled, double-blind study, Canfield reported that five of 12 patients treated with placebo were symptomatically improved without accompanying biochemical changes after six months of therapy.[112] As with calcitonin therapy, biochemical and symptomatic remissions induced by EHDP therapy may be associated with improvement in functional abnormalities such as the high cardiac output state.[42] Although scintigraphic findings may improve with therapy,[108,114,118,119] accompanying radiographic improvement generally does not occur.[112,114,119]

Maximal biochemical and clinical responses seem to be reached by the end of six months of EHDP therapy.[111] After the discontinuation of treatment, prolonged biochemical and clinical remissions up to two years in length have been reported.[111-113,116-118] Length of remission has been found to be inversely related to the pretreatment severity of the disease; patients with the most pronounced baseline elevations of alkaline phosphatase and hydroxyproline tend to show the earliest relapse. Length of remission has also been related to the daily dose of EHDP, but does not seem to be related to the duration of EHDP therapy; the higher doses of EHDP seem to produce longer biochemical remissions.[111,118] No apparent resistance has been noted when additional courses of EHDP have been used to treat biochemical or clinical relapses.[114,115]

EHDP may cause abdominal cramps and diarrhea in a minority of patients. The use of high-dose EHDP over a period of several months has been linked to the development of disabling bone pain in a large number of patients. The bone pain is said to differ in character from that due to the original pagetic involvement. Biopsy specimens of bone taken at the time of the development of the new pain have shown widened osteoid seams suggestive of a mineralization defect.[111,112,118] The bone pain usually resolves within three to six months after the discontinuation of EHDP therapy, although the mineralization defect seen in biopsy specimens may persist for ten months or longer.[115,117] This mineralization defect, which has been found with as low a dose as 7.5 mg per kg of body weight per day, may be associated with an increased risk of bone fracture,[112,115] as well as delayed fracture healing.[114] It has been suggested that 5 mg per kg per day of EHDP is an optimal dose to provide clinical and biochemical benefit while avoiding gastrointestinal side effects and impaired mineralization.[111,112]

Plasma phosphate has been found to be mildly elevated during therapy with high doses of EHDP.[112,116-118,120] The cause of this reversible elevation remains unclear, although phosphate infusion studies have suggested that EHDP may influence both the renal tubular handling of phosphate and the size of the "phosphate space."[120] EHDP does not seem to have a consistent effect on serum calcium levels or on circulating levels of PTH, calcitonin, growth hormone, cortisol or thyroid hormone.[120]

As previously noted, the only diphosphonate utilized widely to date has been EHDP. Early studies on two other diphosphonates, however, have suggested that they also may be clinically useful. Disodium dichloromethane diphosphonate (Cl_2MDP) has been shown to be more potent than EHDP in inhibiting bone resorption *in vivo*.[109] Aminohydroxypropane-diphosphonic acid (APD) has been shown to be more potent than EHDP in the inhibition of bone resorption in Wistar rats, while having less effect on bone mineralization. Short-term studies with APD in the treatment of two pagetic patients have produced encouraging biochemical and clinical results, although histologic results have yet to be reported.[121]

Mithramycin and actinomycin D are related antibiotics that block DNA-dependent RNA synthesis and are cytotoxic. In 1964 intraperitoneal injection of actinomycin D in mice was shown to block the effect of PTH and vitamin D on bone.[122] *In vitro* studies with mithramycin showed inhibition of both bone resorption and osteoid formation.[123] In 1969 and 1970 Ryan and associates reported experience with mithramycin in the treatment of 15 pagetic patients.[124,125] Mithramycin was administered as an intravenous infusion in a dose of 25 μg per kg of body weight per day for a total of ten days. Amelioration of symptoms was associated biochemically with a fall in alkaline phosphatase and hydroxyproline as well as a decrease in bone accretion rate.

Transient hypocalcemia and hypophosphatemia with a concomitant increase in circulating PTH have been noted during mithramycin therapy, but these abnormalities tend to resolve within 48 to 72 hours of the discontinuation of therapy.[124,126] Mithramycin may cause transient nausea and vomiting, but may also exert toxic effects on liver, kidney and platelets. With the doses of mithramycin used, hepatotoxicity has been reflected in transient serum elevations of isocitric dehydrogenase, but no evidence of persistent hepatic dysfunction has been noted. Nephrotoxicity, manifested by transient elevation of blood urea nitrogen (BUN), has been noted in approximately 5 percent of patients; BUN tends to return to baseline over a period of one to two weeks. No consistent effect on platelet count has been observed with the dose of mithramycin employed.[127]

Although sustained biochemical and clinical remissions, with associated improvement in scintigraphic findings, have been reported after inpatient treatment as described above,[24,125,128] a variety of outpatient regimens utilizing periodic infusions of mithramycin has also been successfully used.[129] Clinical studies of the efficacy of actinomycin D have shown biochemical and clinical results similar to those described with mithramycin.[130,131]

Although the treatment of Paget disease in the last decade has largely revolved around the use of the calcitonins, diphosphonates and cytotoxic agents, other treatment modalities have been employed in a handful of patients with reported success. Sekel treated nine patients with daily infusions of calcium gluconate for ten days, reporting symptomatic relief that persisted up to 16 weeks in eight of the patients. A concomitant decrease in alkaline phosphatase of at least 30 percent was noted, although no consistent change in histologic appearance on bone biopsy was found.[132] The successful therapeutic use of exogenous calcitonin led to speculation that glucagon might prove to be clinically useful through release of endogenous calcitonin. Glucagon infusion was used in two patients for 9 and 18 days with rapid clinical and biochemical response, although no increase in circulating calcitonin was detected.[133] Christiansen reported similar success in a single patient treated with daily subcutaneous injections of zinc-protamine-glucagon, although initial therapy with relatively large doses was associated with hypertension and mental imbalance.[134] Evans also attempted to stimulate endogenous calcitonin and suppress endogenous PTH with a regimen designed to produce mild hypercalcemia and hypophosphatemia. A low phosphorus diet was combined with orally given calcium supplements, aluminum hydroxide and a thiazide diuretic. Nine patients treated for 200 days all showed improvement in bone pain associated with a modest but significant increase in serum calcium and a 40 percent fall in alkaline phosphatase; no change in serum phosphorus was noted.[135]

Each of the major therapeutic modalities utilized to date has had features limiting widespread clinical use. Calcitonin must be administered parenterally and frequently has been associated with biochemical rebound, while EHDP has produced bone pain and a mineralization defect in high doses. Mithramycin must also be given parenterally, and has produced at least transient evidence of hepatic and renal toxicity. These limitations have suggested the use of combinations of agents in relatively low doses in an attempt to minimize the toxicities of the individual drugs. While experience has been very limited to date, salmon calcitonin and mithramycin have been used sequentially as well as concurrently with generally favorable results. The combination of mithramycin and glucagon has shown no definite advantages.[136,137] Preliminary evidence suggests that the combination of relatively low doses of EHDP and calcitonin produces a better biochemical response than do higher doses of the individual agents used either alone or sequentially. Bone biopsy studies on patients treated with this combination, which included EHDP in a dose of 7.5 mg per kg per day, showed no evidence of a mineralization defect.[110,138]

Etiology

In his original description of osteitis deformans, Sir James Paget suggested that the primary pathophysiologic process was inflammation.[3] Over the following 50 years, proposed causes for Paget disease included bacterial infection, intoxications with mineral acids, vasculitis, and hereditary and acquired syphilis.[2] It was also argued that the observed bone changes were secondary to a degenerative neurologic process, or that autonomic dysfunction leading to increased skeletal blood flow might be the primary disturbance.[2,47] Parathyroid hormone was also speculated to play a role in the development of the bone abnormalities, although Paget disease has been described in a 61-year-old man with idiopathic hypoparathyroidism.[139]

In 1944 Reifenstein and Albright pointed out that pagetic changes might be widespread, but were not generalized. This histologic observation was felt to be strong evidence against the presence of an underlying metabolic or endocrinologic disorder.[17]

The familial aggregation of cases of Paget disease has been reported, including five pairs of affected idential twins.[140-142] McKusick has argued that the data are consistent with an autosomal dominant pattern of inheritance.[141] A similar viewpoint has been taken by Fotino and associates, who have presented evidence of linkage of Paget disease with HLA haplotype,[143] although evidence on this point has been contradictory. The association of Paget disease with vascular calcification, intracardiac calcification, pseudoxanthoma elasticum and a variety of ocular abnormalities including angioid streaks has led McKusick to speculate that Paget disease may be an abiotrophy of collagen, with the pattern of skeletal involvement dictated by mechanical stresses over a period of time.[141] In studies on 11 untreated pagetic patients, Francis and Smith identified abnormalities in the polymeric collagen fraction extracted from skin.[144] Misra noted abnormal cross-linkage of collagen in bone biopsy specimens from pagetic patients; in a single patient followed with serial biopsies, the cross-linkage was observed to revert to normal after two months of treatment with calcitonin.[145] Although these observations would tend to support McKusick's hypothesis, they have yet to be confirmed.

Another possible cause of Paget disease was suggested by Rasmussen and Bordier, who felt that the histologic heterogeneity observed in osteoclasts and osteoblasts might reflect a benign neoplastic process, the primary event being the activation of an abnormally large number of osteoprogenitor cells.[76]

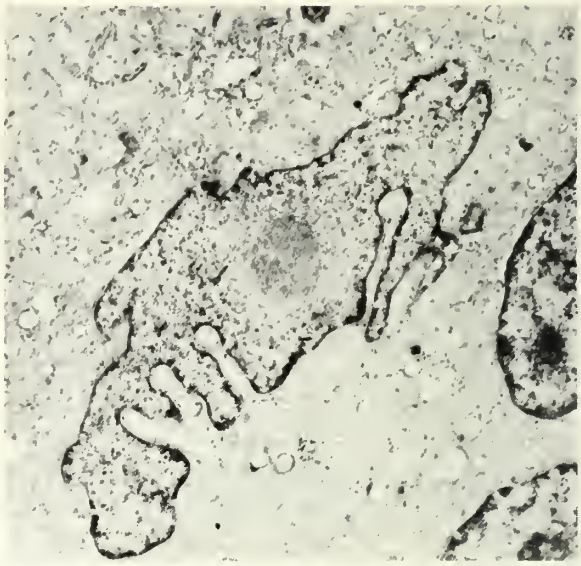

Figure 5.—Nuclear inclusion in the center of an osteoclast nucleus. The inclusion is made up of numerous microfilaments that have a diameter of 150 Å. It is a characteristic feature of osteoclasts in Paget disease. (Reproduced by permission of the publisher from Singer FR[18]).

Perhaps the most intriguing hypothesis on the cause of Paget disease has emerged from electron microscopic examination of biopsy specimens of bone. Investigators have reported the presence of characteristic fibrillar intranuclear inclusions, as shown in Figure 5, in the osteoclasts of every one of 50 pagetic patients studied, both before and after a variety of treatments. The inclusions, which have occasionally been identified in the cytoplasm as well, resemble viral nucleocapsids of the measles type. Similar inclusions have been reported in cases of giant cell tumor of bone, a tumor associated with Paget disease, but have not been found in normal controls or in patients with a wide variety of other bone diseases.[75,146-148] The significance of the inclusions remains uncertain, but the presence of a slow virus infection might explain the observed cases of familial aggregation as well as the tendency of Paget disease to affect older patients.[9]

Despite the above suggestive information on the causes of Paget disease, and considerable success with a variety of somewhat empiric treatment modalities over the past decade, the fundamental

nature of the disease remains little clearer now than at the time of Paget's original description just over a century ago.

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Important Advances in Clinical Medicine

Epitomes of Progress — Allergy

The Scientific Board of the California Medical Association presents the following inventory of items of progress in allergy. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in allergy which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Allergy of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Allergic Bronchopulmonary Aspergillosis

First described in 1952, allergic bronchopulmonary aspergillosis is being recognized with increasing frequency. The disease results from a hypersensitivity reaction to antigens derived from Aspergillus fungi which colonize the bronchial tree without tissue invasion.

The primary diagnostic criteria for this syndrome include (1) episodic bronchial obstruction (asthma), (2) peripheral blood eosinophilia, (3) immediate-type skin reactivity to Aspergillus antigens, (4) serum precipitating antibodies against Aspergillus antigens, (5) elevated serum IgE, (6) history of fixed or transient pulmonary infiltrates and (7) central bronchiectasis. Secondary diagnostic criteria include (1) the finding of Aspergillus in sputum or bronchial washings, (2) history of expectoration of brown plugs and (3) Arthus-type skin reactivity to Aspergillus antigens. Pathologically, allergic bronchopulmonary aspergillosis may show features of microgranulomatosis, mucoid impaction of bronchi, eosinophilic pneumonitis, bronchocentric granulomatosis or combinations thereof.

The disease should be considered in the differential diagnosis of any patient with asthma, eosinophilia and pulmonary infiltrates. There are no pathognomonic diagnostic criteria but the presence of the first six primary criteria determines the diagnosis with reasonable certainty. Proximal bronchiectasis tends to confirm the diagnosis although it may be absent early in the course of the disease.

In addition to morbidity from acute episodes, failure to make the diagnosis results in irreversible complications which include pulmonary fibrosis and bronchiectasis. The treatment for acute episodes and presumably for prevention of complications is administration of corticosteroids, though there are presently no established guidelines for optimal dosage or duration of therapy.

In addition to clinical findings, the serum IgE level may reflect disease activity, falling with appropriate treatment and rising before clinical relapse. As suggested by the immunologic findings in this disease, the immunopathogenesis probably involves both IgE-mediated or Arthus reaction and immune-complex mechanisms. The possible additional role of cell-mediated immunity remains to be clarified.

MICHAEL SCHATZ, MD
ROBERT N. HAMBURGER, MD

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Schatz M, Patterson R, Fink J: Immunopathogenesis of hypersensitivity pneumonitis. J Allergy Clin Immunol 60:27-37, 1977

Primary Immunodeficiency in Adults

ALTHOUGH MANY of the syndromes associated with primary immunodeficient states were described in infants and children, it has become increasingly evident that immunodeficiencies not secondary to other diseases occur also in adults. Most of these patients have either a selective IgA deficiency (<0.05 mg per ml of serum) or a more global deficiency. The latter are placed under the heading "common variable immunodeficiency," defined by a World Health Organization classification committee in 1971 as a heterogeneous group of disorders characterized by hypogammaglobulinemia and susceptibility to infections but variable with respect to age of onset, patterns of clinical manisfestations and presence of cellular immune dysfunction. Although the immunoglobulins are produced by plasma cells derived from B (bursal equivalent) lymphocytes, most of the patients are not deficient in these cells. The defect appears to be in secretion of immunoglobulins. T suppressor cells, decreased T helper activity, a serum inhibitory factor and a missing serum factor have been detected in various patients.

The clinical presentation may be more similar than different in both groups. Sinopulmonary disease is common, a result of recurring infections with common pyogenic organisms leading to chronic sinusitis, recurring pneumonias and to peripheral bronchiectasis. Some patients develop a sprue-like illness and autoimmune diseases such as systemic lupus erythematosus and pernicious anemia. Food and drug reactions are relatively frequent.

Patients with common variable immunodeficiency usually have more serious pulmonary disease than those with only IgA deficiency, and they have a propensity for neoplasia. In one series, 16 percent developed malignancies, three fourths of which were of the epithelial type and the remaining lymphoreticular. Since many of these manifestations have in the past been considered evidence of immunological excess and treated with immunosuppressive agents, this viewpoint needs to be reassessed in light of the findings in primary immunodeficiency in adults.

HAROLD S. NOVEY, MD

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Reactions to Food Additives

IN 1959 Lockey reported the cases of three patients who developed urticaria from tartrazine yellow, an azo dye in their steroid medications. He noted that the same dye is used also for coloring foods, wool and silk. In the past 20 years additional reports have appeared implicating tartrazine yellow as a cause of urticaria, angioedema, asthma, or occasionally a violent systemic reaction. Although many of the reported cases have not been thoroughly documented, a large number of the tartrazine-reactive patients have a history of aspirin sensitivity and nasal polyps.

In 1969 Chaffee and Settipane reported the case of a patient with attacks of asthma and angioedema from the food preservative sodium benzoate, as well as from aspirin and tartrazine. Juhlin and co-workers did provocative oral challenges on eight patients with aspirin-sensitive asthma and found that seven reacted to tartrazine and two to sodium benzoate, and of 52 patients with chronic recurrent urticaria 35 developed hives after challenge with aspirin, 19 reacted to tartrazine and 22 to sodium benzoate. Other investigators have reported a considerably lower prevalence of reactors to these chemicals. Stenius and Lemola found that 25 of 140 asthmatic patients had a positive bronchoconstrictor response to challenge with tartrazine, although only 9 of these gave a history of aggravation of their asthma after ingestion of foods and drugs known to contain tartrazine, and another 7 patients with such a history gave a negative response to deliberate challenge.

Recently Freedman has added sulfur dioxide, a preservative used in orange drinks, to the list of additives causing asthma. This compound, which for years has been known to aggravate asthma when inhaled, caused bronchial constriction within two minutes when given by ingestion, and the effect was blocked by cromolyn sodium.

The mechanism by which these chemical additives cause asthma or urticaria is unknown. There is no evidence that immunologic hypersensitivity is involved, and because of the strong association with aspirin sensitivity it is probable that a nonimmunologic mechanism is involved in reactions to aspirin and the food additives. Several possible modes of pharmacologic idiosyncrasy have been proposed to account for aspirin-sensitive asthma. At present the prevailing theory of aspirin sensitivity is based on the known ability of aspirin

to inhibit the biosynthesis of prostaglandins. Preferential inhibition of prostaglandin E synthesis in the lung, permitting the action of prostaglandin $F_{2\alpha}$, a potent bronchoconstrictor, to remain unopposed, would explain the asthmatic response. The mechanism underlying urticaria and angioedema provoked by aspirin could be a different one, although the role of prostaglandins has not been excluded. In many patients with chronic urticaria, aspirin seems to act as a nonspecific potentiator. The results of experiments to study the effect of tartrazine, benzoates and sulfur dioxide on prostaglandin biosynthesis will be eagerly awaited.

Feingold has proposed that many unspecified food additives and "natural salicylates" may cause hyperactivity and learning disabilities in some children. This theory has gained popular support, but several recent controlled studies of his additive- and salicylate-free diet have shown equivocal or no improvement in children with these disorders.

Food additives, numbering in the thousands, are widely employed to alter the color, taste, and texture of the food and to preserve freshness and inhibit contamination. It is therefore not surprising that some patients may exhibit idiosyncrasy or allergy to one or more of these substances.

ABBA I. TERR, MD

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The Use of Antihistamines in Bronchial Asthma

ANTIHISTAMINES have been considered to provide either no benefit or even to be contraindicated in all asthmatic patients. However, recent studies have shown that these drugs do not necessarily cause a deterioration of the asthmatic state, and in fact may provide benefit. Antihistamines not only block H_1 receptors and thus partially block allergen induced bronchospasm, but they appear to have an anticholinergic effect as well. Popa has reported that high doses of chlorpheniramine given intravenously result in a significant degree of bronchodilation in asthmatic patients without atropine-like side effects. Furthermore, Karlin and co-workers have shown improved pulmonary function in patients with mild asthma receiving twice the usual recommended dosage. No adverse effects were seen in patients with chronic severe asthma receiving antihistamines for coexisting allergic rhinitis or urticaria.

These recent studies warrant the following conclusions:

- Asthmatic patients with allergic rhinitis may safely receive antihistamines in the usual dosage, and there is no evidence that coexisting asthma will be exacerbated.
- Although antihistamines can improve asthma in some cases, their use in asthmatic patients must be established on an individual basis.
- The use of antihistamines in patients with status asthmaticus cannot be recommended at this time because of the existence of more effective drugs and because potential drying effect of antihistamines on bronchial mucus has not been firmly clarified.

STANLEY P. GALANT, MD
LAKSHMI DURISETI, MD

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The Measurement of IgE

THE AMERICAN ACADEMY OF ALLERGY has appointed a Committee on Standardization of In Vitro Tests which is charged with defining and correcting the problems in the quantitation of IgE. They conducted a nationwide single-blind evaluation of the accuracy and reproducibility of the quantitation of IgE which showed an unacceptable level of variation. Besides the large variation between laboratories, the variation of repeated assays within laboratories was unacceptably large.

Part of the problem is undoubtedly due to differences in assay methods. A study of the various assay methods—radioimmunosorbent test (RIST), double-antibody radioimmunoassay (RIA), radial immunodiffusion (RID) and paper disc immunosorbent test (PRIST)—shows that RIST and RID may lead to spurious elevations of IgE in sera and secretions. Double-antibody RIA and PRIST provide the best agreement, but PRIST may give deceptively low results in certain sera. When all 14 laboratories assayed the test serum with the PRIST kit, variations within and between laboratories (133 units per ml to 330 units per ml) were still more than 2½ fold. The problems of the quantitation of IgE are being resolved and a "predictive" table of serum IgE levels in infants,

children and adults, such as the one that follows, may be of value.

IgE—units per ml				
	Children and Adults			
Infants <2 yrs.	>3 yrs. (RIA)	(PRIST)	Percent of the Population	Allergic Percent
<10	<100	<65	68	<5
10-20	100-350	65-230	20	20
21-100	351-750	231-500	9	35
>100	>750	>500	<3	~100*

*In the absence of helminthiasis.

ROBERT N. HAMBURGER, MD

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Occupational Asthma

OCCUPATIONAL ASTHMA refers to a disease in those persons in whom asthma develops primarily from exposures at their work or hobby sites. Although occupational asthma dates at least to Ramazzini's reports in 1700 of asthma provoked by flour dust in bakers and wig makers, the sources of exposures seem to be on the increase in recent years. The provoking agents may be divided into those of (1) *animal origin* affecting poultry farmers; veterinarians; horse, cattle and sheep breeders; chicken inspectors; furriers, and aviarists; (2) *vegetable origin:* farmers, hempworkers, grainworkers, bakers, millers and woodworkers; (3) *inorganic chemicals:* chromium, platinum, aluminum and nickel factory workers, electricians, welders and solderers, and (4) *organic chemicals:* plastic makers and painters who handle isocyanates; meat wrappers exposed to polyvinyl fumes; workers in pharmaceutical plants, and workers using enzymes such as trypsin, Bacillus subtilis enzymes and papain. These are but a few examples of an almost endless list of occupations and causative agents in occupational asthma.

Asthma may occur not only in those who are predisposed by being atopic but also in apparently normal persons without a personal or family history of allergies or IgE specific antibodies. There is some evidence that the atopic persons have a more rapid onset of symptoms following exposures and tend to leave their jobs sooner. Asthma may occur within minutes of a sufficient exposure and responds well to bronchodilators. Others may have asthma delayed several hours after exposure and are better controlled by steroids than by epinephrine or theophylline. Some experience both immediate and late onset asthma.

The pathogenic mechanisms are not always clear-cut. Some agents such as animal danders and enzymes are allergens producing specific IgE antibodies even in nonatopic persons. Others such as polyvinyl and acetylene fumes are respiratory irritants, while still others like toluene diisocyanate (TDI) may have both antigenic and irritant properties.

The examining physician can be alerted to the relationship of asthma to job or hobby by obtaining a careful history. A tip-off is the waxing and waning of symptoms, worse during workdays and better on holidays, weekends and vacations. Sometimes the exposure source may not be readily apparent, such as the case of a secretary whose office is clean but who shares access or ventilation with an adjoining factory. Confirmation that the suspected agent does provoke asthma may require bronchial challenge and immunological studies on the patient and control subjects. Discovery of occupationally induced asthma is rewarding, since removal from the exposure may well effect a cure.

HAROLD S. NOVEY, MD

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Pepys J: Clinical and therapeutic significance of patterns of allergic reactions of the lungs to extrinsic agents. Am Rev Respir Dis 116:573-588, Oct 1977

Emergency Room Treatment of the Adult Asthmatic

DURING THE COURSE of chronic asthma, acute attacks occur that can be effectively treated in a hospital emergency room. A brief initial history can determine the possible precipitating cause of the attack, such as exposure to allergens or respiratory irritants, intercurrent viral respiratory infections, aspirin or other analgesics, emotional trauma, inadequate maintenance therapy, abrupt withdrawal of steroid medications, or overuse of aerosol bronchodilators.

Severe bronchial obstruction produces decreased breath sounds, notably prolonged expiration, use of accessory muscles of respiration and pulsus paradoxus. Tachycardia and mild hypertension are characteristic of acute asthma and not necessarily complications of treatment. Cyanosis, quiet chest, restlessness and exhaustion are ominous signs of impending or actual respiratory failure

Arterial blood gas measurements are essential

for determining optimal treatment. In uncomplicated mild to moderate asthma, hypoxemia secondary to ventilation-perfusion abnormalities stimulates hyperventilation resulting in a low arterial carbon dioxide pressure (P_aCO_2) and elevated pH. Normal or elevated P_aCO_2 indicates need for immediate admission to hospital. Pronounced carbon dioxide retention associated with signs of respiratory insufficiency may require immediate intubation and mechanical control of ventilation in a pulmonary intensive care unit.

If the patient has not already used sympathomimetic drugs excessively, injection of aqueous epinephrine 1:1,000, 0.2 to 0.5 ml given subcutaneously, should lead to rapid improvement, and this dose can be repeated in 30 minutes if necessary. Terbutaline, 0.5 ml given subcutaneously, is theoretically less cardiotoxic, although its superiority over epinephrine in the emergency room treatment of asthma has not yet been established.

Intravenously given aminophyllin should also be used immediately. If no aminophyllin had been taken in the preceding eight hours, an initial loading dose of 5.6 mg per kg of body weight can be given over 20 minutes, followed by an infusion of 0.9 mg per kg of body weight per hour to achieve a therapeutic serum theophyllin level of 10 to 20 mg per liter. This dose must be lowered if the patient had been taking aminophyllin orally or has evidence of cardiac or hepatic disease.

The need for corticosteroids must be judged on an individual basis. Intravenously given hydrocortisone or methylprednisolone is mandatory if respiratory insufficiency is present or if the attack was caused by abrupt withdrawal of previous steroids or bronchodilator aerosol abuse. Nasal oxygen is given to correct hypoxemia, and blood gas determinations are repeated in 20 to 30 minutes and thereafter as indicated by the clinical improvement. There is no indication that asthmatic attacks are caused by bacterial respiratory infections, or that antibiotics are useful in the acute attack.

The effect of treatment can be assessed by repeated auscultation of the chest, but a simple test of ventilation, such as peak expiratory flow rate (PEFR) as determined by a Wright Peak Flow Meter, can be very helpful. Banner and coworkers recently showed that failure to improve PEFR by 15 percent immediately and 42 percent at the end of emergency room treatment probably indicates the need for admission to hospital.

Administration of sympathomimetic drugs by intermittent positive pressure breathing (IPPB) in acute asthma is controversial, and the dangers are significant. Karetsky recently reported the cases of two patients who died from subcutaneous emphysema and pneumothorax during the course of such treatment for acute asthma.

At the conclusion of the emergency room visit, arrangements should be made for follow-up management to prevent recurrences. It has been well documented that small airway obstruction can persist for days and weeks after clinical signs of the acute attack have cleared completely. Regular continuing outpatient management of asthmatic patients significantly reduces the need for emergency room visits.

ABBA I. TERR, MD

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EDITORIALS

Clinical Algorithms

ALTHOUGH IT WAS NOT APPARENT at the time, the introduction in the early 1970's of clinical algorithms or protocols[1-4] had a significant impact on health services research and delivery. These clinical algorithms were designed to guide new health practitioners (NHP's) though areas of health care delivery previously reserved only for physicians. Because they were based not only on collection of data but also on the use of the results of historical, physical and laboratory inquiry, they represented a conceptual departure from "guidelines" for care and conventional clinical teaching. Now, medical reasoning was exposed and found to be transferable to nonphysicians. The breakthrough was not in giving NHP's responsibility for diagnosis and patient management; the management by NHP's of patients had earlier been shown by Lewis and Resnick to be effective and safe.[5] Rather, the major and more important effect was the introduction of the science of physician decision-making into the clinical literature and into the consciousness of physicians.

With the exception of occasional clinically oriented approaches to the analysis of physician decision-making,[6] most approaches, especially those that were computer-based, were viewed as too complicated for use by clinicians. When the initial studies regarding algorithms were published, the black box was opened: there was indeed an understandable science of medical diagnosis that underlay the skills of our legendary teachers of bedside medicine. Diagnostic elements of the history and physical examination were shown to possess, like laboratory tests, quantifiable properties such as sensitivity and specificity. Their use required value judgments of which we were often not aware.[7]

Apart from the individual criteria and standards for the history, physical examination and laboratory tests, the entire workup, as a set of clinical strategies presented as a protocol, was an instrument greater than the sum of its parts. This instrument could be rigorously evaluated through various types of clinical studies, including randomized controlled trials.[3,8-10] That algorithms have become incorporated into medical consciousness is evidenced by such examples as the recent series, "Toward Optimal Laboratory Use," published in *JAMA*,[11] and the transformation of the algorithm approach into a retrospective mode for quality of care assessment.[12,13] Clearly, the protocol/algorithm movement was one of the strands that merged with other developments to form the now emerging field of clinical epidemiology or clinical health care delivery.

Conte's paper elsewhere in this issue of the WESTERN JOURNAL must be viewed in this historical perspective. It represents a replication of other work, the standard approach in scientific medicine but rare in health services research. It tells us, though not in the controlled fashion of a randomized trial, that the combination of NHP's and protocols can provide good medical care that is not specific to a few situations; in other words, that this combination is generalizable. The study design could be more rigorous in several aspects: blinding the MD's to the NHP findings, comparing the NHP-protocol care to an independent standard of physician care, comparing times and costs in a more exacting (not self-reported) way. Nonetheless, the critical dimensions of a health care delivery measure have been addressed: reproducibility of findings, effectiveness (in terms of urine culture, symptom relief or physician agreement), costs, and acceptability by patients.

Does this kind of research threaten us? Do protocols automate care and deny its art? Do they oversimplify the complexity, the richness of

the clinical encounter? Our experience five years after the introduction of these new instruments tells us that clinical medicine is not diminished by making strategies explicit. Collecting reliable data, appreciating the psychological nuances of care, understanding when to deviate from the protocol to account for patients not included in the branches—these skills still demand good judgment, wisdom, experience and compassion. Perhaps protocols, by lending confidence to a provider, may enhance the art of medicine.

Much needs to be done, even for relatively simple ambulatory problems, such as dysuria. The inclusion of individual historical items, the physical examination elements, and laboratory tests must be shown to improve care. The recent finding that a diagnosis of vaginitis is twice as likely as a diagnosis of urinary tract infection in women with dysuria can lead to better understanding of medical processes.[14] The clinical algorithm/protocol field has lent impetus to the kind of study that yielded this finding. Eventually, the evaluation of the efficacy of various medical processes will result in optimum clinical strategies and improvement of medical care practice by both NHP's and physicians.

SHELDON GREENFIELD, MD
Associate Professor of Medicine and Public Health
University of California, Los Angeles

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A Unique and Useful Memorial

A FEW MONTHS AGO a dedicated and compassionate young physician was killed in a tragic automobile accident in Los Angeles where he was in residency training. A future which surely held great promise for both medicine and society suddenly was no more. His physician father has found a unique and useful way to perpetuate a memory and perhaps to keep alive something of what that young physician stood for and sought to do with his life. A fund has been established at the School of Medical Sciences, University of Nevada, in memory of Fred M. Anderson, Jr., MD. This fund will provide subscriptions to THE WESTERN JOURNAL OF MEDICINE for students at the University of Nevada School of Medical Sciences. Thirty-eight third-year medical students are to receive the journal beginning with this issue. Next year it is hoped that 48 more students and approximately 20 residents will be added. THE WESTERN JOURNAL OF MEDICINE is honored to be chosen as the vehicle for such a living memorial to a fine young physician, and its editors are humbled by the trust that has come to them.

—MSMW

Role of Hyperglycemia in the Progression of Diabetic Vascular Disease

MANY, IF NOT ALL of the complications of diabetes mellitus were known to experienced clinicians in the latter half of the 19th century. Naunyn's treatise published in 1896 describes the various forms of neuropathy, the close association to arteriosclerosis, and the vascular changes in the retina.[1] The delineation of the specific lesion of nodular glomerulosclerosis and the classification which sorted out small vessel from large vessel disease came only within the last 50 years.[2,3] At present diabetic nephropathy and retinopathy are thought to result from (and begin with) basement membrane overgrowth accompanied by cell degenerations (for example, mural cells and the like).[2,4,5]

Some instances of neuropathy may well be

the sequelae of diabetic capillary disease of the nutrient vessels; other cases are thought to result from altered glucose handling by the nerve sheaths and consequent osmotic damage.[6-8]

The atherosclerotic lesions in diabetes cannot generally be distinguished histologically from those in nondiabetic persons. However, they develop earlier in life and their progression is more rapid.[9,10]

Lack of insulin per se clearly is not the cause of the vascular complications. Their frequency and severity have increased greatly following the successful use of insulin; many persons were saved from death by coma and severe infections only to experience vascular deterioration.

Since the 1950's we have known that most diabetic persons (the milder obese type) do not suffer from insulin lack.[11-14] They are insulin resistant in some areas of this hormone's action (liver and muscle); but not in respect to other effects (lipogenesis, antilipolysis, adiposity).

Over the years, many diabetologists have come to the conclusion that the prevention of onset and reduction in severity of the vascular lesions were related to the degree of control of the blood glucose level. Other observers were not convinced by the available data. These are difficult to validate and contradictions abound.[15-17] Mechanisms other than hyperglycemia have been suggested: growth hormone excess,[18] glucocorticoid effects,[19] deposition of immune complexes[20] and others. The precise causal relationships between hyperglycemia and vascular damage remain unresolved.

Mayer Davidson in the Medical Progress elsewhere in this issue has written a thoughtful and reasonable survey of the available data. His interpretation of the experimental and clinical literature is strongly in favor of the virtues of strict control. His suggestions regarding the proper use of insulin to achieve better control are reasonable and sound.

However, it must be pointed out that some of Dr. Davidson's deductions and expectations reach farther than may be warranted. Some pathologists will balk at accepting the retinal and glomerular lesions of experimentally diabetic rats as authentic analogues of the human condition. The data collected by a group in Paris which are said to show the beneficial effects of multiple versus single insulin injections on the progression of retinopathy, are beclouded by small numbers, poor controls and dubious statistical handling.[21]

The larger issue of the effects of chronic hyperglycemia on blood vessels will remain unresolved until such a time when it would be possible to achieve 24 hour normoglycemia in a diabetic over many years (islet transplantation or artificial pancreas).

There are two potent theoretical arguments in favor of the view that even mild hyperglycemia (above 120 mg per dl) may be disadvantageous or injurious:

- In the nondiabetic state the existing hormonal regulatory mechanisms maintain the 24 hour blood glucose variations between about 80 and 120 mg per dl. What were the evolutionary selection pressures which dictated such a narrow range? The threat of hypoglycemia may explain the lower figure, but 120 mg is significantly below renal threshold. What injurious consequences may we be preventing by the tight normal blood glucose regulation?
- The chronic maintenance of high blood glucose levels in diabetes leads to the "glycosylation" of normal hemoglobin. Hemoglobin Alc is formed by the addition of glucose to the molecule. Is this unique to hemoglobin or do other proteins (enzymes) undergo similar changes? If so, does this affect their functions in cell metabolism?

Meaningful answers to these problems await our ability to maintain the blood glucose level of diabetic patients in an accurate and predictable fashion over the years.

Until that time arrives it behooves us to regulate the glucose levels in diabetic persons requiring insulin as best we now can, avoiding significant hyperglycemia as well as episodes of hypoglycemia. Dr. Davidson states that his suggested mode of the use of the available insulins, would in most patients, "maintain fasting glucose values below 180 mg per dl and postprandial ones below 250 mg per dl." This is indeed worthwhile in itself, but one needs to be careful not to raise hopes inordinately that such a regime would definitely prevent the onset or progression of vascular complications.

In view of the fears generated in the community in regard to undesirable actions of the available oral hypoglycemic agents, there has been a growing tendency to use *insulin* to control the blood glucose levels of *obese* persons with adult-onset diabetes. This is not the most desirable mode of therapy for this group, since there is much circumstantial evidence of the proatherogenic effects of high amounts of insulin.[22-26] In

this group the best approach is the admittedly tedious and difficult regimen of caloric reduction and physical exercise.

It would appear that as much research effort as possible should now be directed to the attempts at successful islet transplantation or the provision of a continuous regulated insulin supply, or both, for patients with severe diabetes. Only then will we be in a position to take a definitive stand towards the issue of strict control and its benefits.

RACHMIEL LEVINE, MD
Director
Department of Metabolism and Endocrinology
City of Hope National Medical Center
Duarte, California

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A Perspective on Health Care Costs

IN ALL THE HUE AND CRY about health care costs it is often overlooked that these costs actually reflect a remarkable degree of success in achieving a national goal. Some will remember that shortly after World War II there was a definite determination to invest more of the nation's resources in health and health care for our citizens. With the use of unlimited dollars impressive technology had been developed for destructive war purposes, and when the war was won it seemed reasonable and desirable to turn this capability to a constructive purpose which would benefit people. Better health and health care became a national goal. What has been accomplished is one of the great success stories of our times.

At first substantial public and private resources were allocated to medical research and the development of new technology. Subsequently, the health care that was developed with this new knowledge and new technology was declared to be a right to which all citizens should have equal access. New and sophisticated diagnostic and therapeutic procedures have been developed which allow for greatly improved management of such conditions as heart disease and many forms of cancer. Advanced life support systems have become available in general and community hospitals throughout the country. And life support for victims of end-stage renal disease has become possible and its very substantial cost has been assumed by the federal government. These are only some of the scientific and technologic advances that have added to the cost of health care.

Much has also been accomplished in implementing the right of equal access to health care and, as might have been expected, this has substantially increased the amount of care rendered and thus the total cost. Government programs such as Aid to Crippled Children, Medicare, Medicaid, and more recently special programs for handicapped people provide access to better and more costly care for many formerly relatively deprived segments of the population. Private health insurance has provided it for most of the rest. Charity has been almost completely eliminated from mainstream health care. It was considered demeaning. And the compensation of health workers throughout the system has been brought up to parity with workers in other fields

in business and industry. Looked upon in this way, the health care enterprise is truly a success story. The costs which have risen faster than other segments of the economy are seen to be the costs of carrying out the mandates of a major national commitment, and the whole has been a combined, although not always a cooperative, effort of the public and private sectors.

In this perspective it is seen that we have accomplished much of what we as a nation set out to do some 30 years ago. The increment of the costs that is rising faster than other indices in the economy represents the allocation of additional resources from both the public and private sectors to this purpose. But all of this is not to say that the costs of health care should not now be contained. Rather it suggests that it may be time to review what has been accomplished, see where we should go from here, and perhaps most immediately identify and eliminate costs that do not produce a commensurate benefit, whether they be for procedures, services, facilities or administration, or are costs added by government regulation. This too will have to be a collaborative effort of the public and private sectors.

Let us hope that the success story in health care will continue and that our national achievement will not be frittered away with crude and clumsy bureaucratic controls. This is a very present danger.

—MSMW

CASE REPORTS

Refer to: Hirshman HP, Schurman DJ, Calin A: Neutropenia and rheumatoid arthritis. West J Med 129:235-236, Sep 1978

Neutropenia and Rheumatoid Arthritis

H. PAUL HIRSHMAN, MD
DAVID J. SCHURMAN, MD
ANDREI CALIN, MD
Stanford, California

THE cause of rheumatoid arthritis remains unknown. It is generally accepted that the pathogenesis involves neutrophils, lymphocytes and other components of the immune system. The opportunity to study the role of the individual cell types in clinical arthritis is rare.

A patient with longstanding unremitting severe seropositive rheumatoid arthritis who developed pancytopenia secondary to chlorambucil therapy has recently been reported. In this patient "the objective signs of arthritis disappeared." This remission was complete and lasted several weeks until the patient's death.[1] The mechanism of the action of chlorambucil in rheumatoid arthritis* is not understood, and the significance of the pancytopenia in the remission is not known. A review of the Stanford University Hospital Immunology Clinic experience with rheumatoid arthritis showed no other patients in whom pancytopenia developed with a leukocyte count of less than 1,000 per cu mm. To find out whether there was clinical evidence implicating a subpopulation of leukocytes in active rheumatoid arthritis, the clinic experience also was to search for patients with selective lymphocytopenia or selective neutropenia (absolute lymphocyte or neutrophil count less than 250 with total leukocyte count greater than 2,500 per cu mm). There were no cases of selective lymphocytopenia. The following report documents our only case of selective neutropenia.

Report of a Case

A 51-year-old woman, with long-standing severe seropositive, erosive, nodular rheumatoid arthritis involving multiple joints, was admitted to Stanford University Hospital on November 18, 1976, with neutropenia and osteomyelitis of her right great toe.

Her rheumatoid arthritis began in 1948. Therapy included salicylates, steroids and reconstructive procedures on both hands.

In 1965 recurrent respiratory and urinary infections developed. The total leukocyte count fell to 2,700 per cu mm, with 63 percent lymphoctyes and 2 percent neutrophils; her spleen was noted to be enlarged. On splenectomy, hyperplasia of the reticuloendothelial system, consistent with the Felty syndrome, was noted. Postoperatively, the leukocyte count rose to 8,900 per cu mm, with 56 percent neutrophils.

Subsequently, for approximately a year, the patient had the only real remission of disease. The neutrophil count remained normal. A routine leukocyte count obtained on September 22, 1976, showed 4,900 leukocytes per cu mm with 33 percent neutrophils.

In October 1976 pain and swelling developed in the patient's right great toe ten days after trauma. She was given tetracycline orally and the toe was incised and drained. Her condition failed to improve and she was admitted to her local hospital on November 5. On admission the leukocyte count was 5,000 per cu mm, with 2 percent neutrophils. Cultures of tissues of the toe grew Proteus morgani, sensitive to cephalosporins, and cephalexin (Keflex®) was administered.

On November 18 the patient was seen at Stanford where radiographs showed osteomyelitis. She was admitted for intravenous therapy with cefoxitin (Mefoxin®), a new cephalosporin. Radi-

From the Department of Surgery, Division of Orthopedic Surgery (Drs. Hirshmann and Schurman), and the Department of Medicine, Division of Immunology (Dr. Calin), Stanford University School of Medicine.

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Reprint requests to: David J. Schurman, MD, Department of Surgery, Division of Orthopedic Surgery, Stanford University School of Medicine, Stanford, CA 94305.

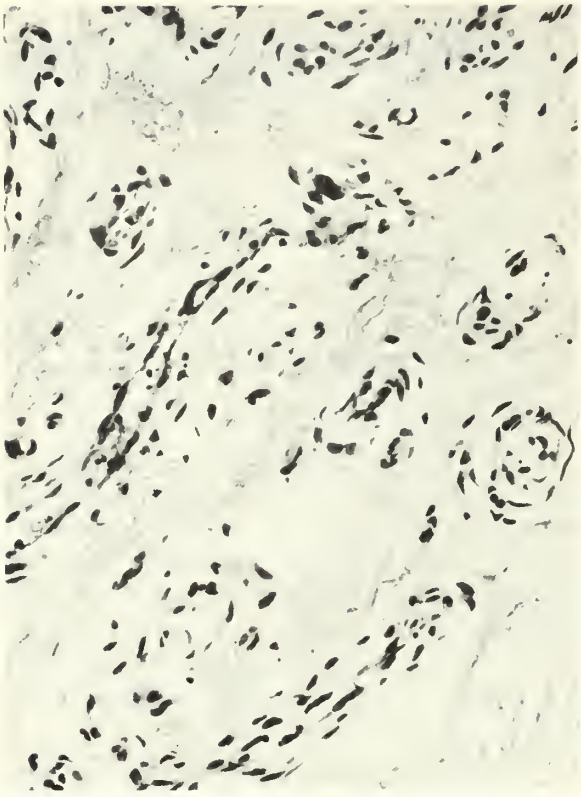

Figure 1.—Well-vascularized tissue from amputated toe shows notable paucity of neutrophils in an area of inflammation.

onuclide scanning did not suggest residual splenic tissue, and the cause of the neutropenia remained unclear. She has never received gold, penicillamine or cytotoxic therapy.

The soft tissue infection responded well to the antibiotic therapy despite persistent neutropenia with leukocyte counts between 5,000 and 9,000 per cu mm and 0.2 percent neutrophils. On November 29, the toe was amputated. Pathologic studies showed few neutrophils even at the site of infection (Figure 1). The wound healed well.

During this entire episode, as during the previous episode of neutropenia in 1965, the patient's rheumatoid arthritis remained active with an aggressive nodular erosive polysynovitis involving elbows, wrists, hands, knees, ankles and feet.

Comments

It is known that arthritis may persist in the Felty syndrome in the face of neutropenia.[2] The present case shows that arthritis may remain active despite a prolonged virtual absence of circulating and tissue neutrophils.

While most of the leukocytes present in the synovial fluid of patients with active rheumatoid arthritis are neutrophils, the cellular infiltration of the synovium is primarily mononuclear. Current concepts of pathogenesis stress abnormalities of the lymphocytes.[3]

The condition of patients with progressive, therapy-resistant rheumatoid arthritis who undergo thoracic duct drainage to achieve lymphocyte depletion improves significantly. After termination of the drainage, lymphocyte counts return to normal levels and arthritis recurs.[4] Extracorporeal irradiation of thoracic duct lymph with reinfusion of the irradiated lymphocytes is similarly effective, presumably because of death of the lymphocytes.[5] Moreover, in rats with adjuvant arthritis (rats are a widely used animal model of rheumatoid arthritis) there is improvement with antilymphocyte globulin treatment.[6]

In our case, very severe and persistent neutropenia, per se, did not appear to alter the clinical course of rheumatoid arthritis. A previous case of pancytopenia[1] was associated with the dramatic disappearance of clinical signs of rheumatoid arthritis. Clarification of the role of leukocytes in the pathogenesis of rheumatoid arthritis may be advanced by additional reports of cases in which pancytopenia or selective leukopenia occurred in patients with active rheumatoid arthritis.

Summary

The pathogenesis of rheumatoid arthritis involves several components of the immune system including neutrophils and lymphocytes. A case has been reported here in which rheumatoid arthritis remained active in the face of very severe and prolonged neutropenia. The literature suggests that lymphocytopenia, on the other hand, results in remission. Further analysis of clinical cases may give insight into the significance of individual components of the immune system in the pathogenesis of rheumatoid arthritis.

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Refer to: Sattler FR, Ruskin J: Bovine pulmonary tuberculosis in adults—A new view of an old infection. West J Med 129:237-240, Sep 1978

Bovine Pulmonary Tuberculosis in Adults

A New View of an Old Infection

FRED R. SATTLER, MD
JOEL RUSKIN, MD
Los Angeles

HUMAN INFECTION due to Mycobacterium bovis was first recognized early in this century. Most cases appeared to result from ingestion of contaminated cow's milk.[1,2] They occurred predominantly in children and were characterized by lymphadenitis, arthritis and osteomyelitis.[2-5] Pulmonary involvement was uncommon. The disease became a rarity in the United States after World War I when rigid surveillance of dairy herds and compulsory pasteurization of milk were instituted.[1,6,7] Only 27 cases were recorded in the United States between 1954 and 1973.[8-15] However, in just the last three years (1974 through mid-1977), seven patients with disease due to M bovis have been identified in Los Angeles County alone. (Personal communication, Seymour Froman, PhD, clinical laboratory supervisor, Olive View Medical Center.)

We considered it of interest to describe in detail one of these cases since it presented clinical features quite distinct from the classic description of bovine tuberculosis alluded to above. First, disease became manifest in the patient in adulthood; second, the expected extrapulmonary involvement was not seen. Rather, the patient had far advanced cavitary pulmonary tuberculosis that one would ordinarily ascribe to infection with Mycobacterium tuberculosis. Furthermore, she was pregnant and to our knowledge, bovine tuberculosis had not heretofore been reported in association with pregnancy. Accordingly, special attention had to be paid to her newborn who was potentially exposed to the infection *in utero* and in the perinatal period.

From the Department of Medicine, Division of Infectious Diseases, Kaiser-Permanente Medical Center, Los Angeles.

Submitted, revised, November 8, 1977.

Reprint requests to: Joel Ruskin, MD, Chief, Division of Infectious Diseases, Kaiser-Permanente Medical Center, 1505 N. Edgemont St., Los Angeles, CA 90027.

Figure 1.—Initial roentgenogram of the chest taken December 26, 1974, shows a thick walled cavity in the right upper lobe. There are also reticulonodular infiltrates present at both lung bases.

Report of a Case

A 28-year-old Mexican-American woman was seen at the Kaiser-Permanente clinic in June 1974 with complaint of a nonproductive cough for one year. Physical examination showed no abnormalities. An x-ray study of the chest was not done, but three months earlier, a routine preemployment chest roentgenogram done at a proprietary hospital was said to give normal findings. The patient was next seen in August 1974 at which time she was found to be pregnant.

She had no symptoms or signs of systemic illness until December 1974, when she reported increasing fatigability, dyspnea upon minimal exertion and, rarely, blood streaked sputum. The patient had not had fever or night sweats. Findings on physical examination again were unremarkable. The hemoglobin value was 13.2 grams per dl and the leukocyte count was 7,700 per cu mm with 68 percent polymorphonuclear cells, 30 percent lymphocytes and 2 percent monocytes. Analysis of urine showed no proteinuria or sedimentation rate abnormalities. Tests of liver function were within normal limits. A chest roentgenogram (Figure 1) showed a thick walled cavity in the right upper lobe and interstitial infiltrates at both lung bases. An intermediate strength (5TU) tuberculin skin test measured 10 mm in diameter and Ziehl-Neelsen stains of expectorated sputum specimens showed acid-fast

Figure 2.—Roentgenogram of the chest obtained January 10, 1975, shows enlargement of the right upper lobe cavitary lesion and increase in the interstitial infiltrates.

bacteria. A diagnosis of pulmonary tuberculosis was made and the patient was treated with 300 mg of isoniazid (INH) and 800 mg of ethambutol per day. Two weeks later a repeat chest roentgenogram (Figure 2) showed enlargement of the cavitary lesion in the right upper lobe and increase in the reticulonodular infiltrates at the lung bases.

The patient's symptoms abated approximately three weeks following initiation of antituberculous therapy. On March 8, 1975, five sputum cultures obtained in January, yielded moderate to heavy growth of M bovis. The organism was identified according to criteria listed in Table 1. When the patient was further questioned about potential sources for her infection, she related that she had been born on a dairy ranch in Guadalajara, Mexico, and had drunk raw cow's milk daily from early childhood until her emigration to the United States in 1972. She denied recent or remote exposure to persons with known tuberculosis. Her husband, her only household or close contact, was healthy and his tuberculin skin test and chest film were negative.

The patient remained well on a regimen of INH and ethambutol and on March 31, 1975, sputum smears were negative for acid-fast bacteria. That day she delivered a 6 pound, 13 ounce term girl; findings on physical examination and chest roentgenogram of the infant were within normal limits. The infant was given chemoprophylactic therapy with INH (10 mg per kg of body weight per day) and was discharged with her mother. Three weeks following parturition the patient's chest roentgenogram (Figure 3) showed significant resolution, and the remainder of her course was uneventful. The infant grew and developed normally; at 12 months of age her 5TU skin test was negative and administration of INH was discontinued.

TABLE 1.—*Criteria Used for Identification of Mycobacterium Bovis*

	Our Patient's Isolates	*M. bovis*	*M. tuberculosis*
Growth characteristics			
Growth rate	35 days	25-40 days	14-25 days
Colonial morphology	Dysgonic	Dysgonic	Eugonic
Biochemical analysis			
Niacin production ..	No	No	Yes
Nitrate reduction ...	No	No	Yes
Inhibited by TCH (Thiophene-2-carboxylic acid hydrazide) .	Yes	Yes	No

Figure 3.—Roentgenogram of the chest taken April 21, 1975, shows significant resolution of the previous pulmonary infiltrates.

Discussion

Early in this century bovine tuberculosis occurred most often in children who characteristically presented with extrapulmonary sites of infec-

tion. In contrast, our patient was an adult in whom infection was manifested by cavitary pulmonary lesions. Therefore, initially she was presumed to have typical tuberculosis. In order to determine whether our case might reflect more accurately the current age distribution and clinical features of M bovis infection, we reviewed 42 well-described cases of bovine tuberculosis reported recently (1954 through 1973) from the United States and Canada.[8-11,14-16] Indeed, all of these cases occurred in adults and 19 (45 percent) of the 42 had significant pulmonary infection. Moreover, six (including our own) of the seven cases reported to the Los Angeles County Health Department since 1974 also occurred in adults and in each of them there was microbiologically documented pleuropulmonary involvement.

The increased incidence in Southern California of disease due to M bovis merits further comment. It is perhaps explainable by the presence in this area of previously infected immigrants who have come from countries where pasteurization of milk was not mandatory. Our patient is a case in point. We suspect that she acquired her infection in rural Mexico by drinking raw cow's milk. The exact prevalence in Los Angeles of imported infection with M bovis is not known. However, in our own institution, the rate of positive Mantoux reactions in pregnant foreign-born Latins and Asians is 41 percent (as opposed to 5 percent in native-born whites and blacks). Given the different social mores and generally substandard economic status of these foreign-born ethnic groups, their higher tuberculin reactivity might well be the result of previous exposure to M bovis rather than to M tuberculosis alone.

It is also noteworthy that the consumption of unpasteurized milk is increasing in the United States as part of renewed interest in "natural foods." One dairy in Southern California now sells approximately 10,000 gallons of raw milk daily. Whether any of the recent cases of bovine tuberculosis in Los Angeles County can be linked to such food preferences is unknown. But we would suggest that in other communities where large quantities of unpasteurized milk are distributed, the incidence of the infection should be carefully monitored.

Since bovine tuberculosis occurring during pregnancy had not been previously reported, it was not clear whether our patient's pregnancy might adversely affect her response to treatment.

TABLE 2.—*Drug Susceptibility Studies*

	*μg/ml**
Para-aminosalicylic acid	2.0
Ethambutol	5.0
Streptomycin	2.0
Isoniazid	0.2
Rifampin	1.0

*The concentration of antibiotic which permits growth of less than 1 percent of a standard inoculum.

However, once chemotherapy was instituted, she showed rapid clinical improvement. This result was not entirely unexpected since pregnancy does not appear to impede control of typical tuberculous infection in appropriately treated patients.[17-20] We assumed that her infection would respond to the same agents utilized to treat M tuberculosis. In fact, her M bovis isolate had excellent *in vitro* sensitivity to the standard first line antituberculous drugs (Table 2). These results are in accord with other studies of the antimicrobial susceptibility of the organism,[14] although an occasional strain may be relatively resistant to para-aminosalicylic acid.[14,21]

The potential risk for development of M bovis infection in our patient's newborn was more difficult to assess. It could be argued that this risk was negligible since the patient was probably noninfective at parturition; she had been receiving chemotherapy for almost three months and had a negative sputum smear for acid-fast bacilli. On the other hand, our initial insecurity about whether she would continue to comply with her therapeutic regimen together with previous published warnings asserting that neonatal infection with M tuberculosis may occur even when mothers are believed to be noninfective[22,23] led us to conclude that the infant did merit some form of antituberculous prophylaxis. Unfortunately, we were unsure as to what would be the most appropriate preventative therapy for M bovis infection. Our decision to use INH for this purpose was entirely empiric, since its chemoprophylactic efficacy had been established only for M tuberculosis infection and in children older than the newborn.[24,25]

Yet, we knew that our patient's M bovis isolate was susceptible to INH and that initiation of drug treatment shortly after delivery might afford the neonate more immediate protection against early acquisition of infection while obviating the need to separate the baby and mother for an unduly

lengthy period (such as that required following neonatal vaccination with bacille Calmette Guérin).[23]

Clearly, until further experience with bovine tuberculosis in pregnancy is obtained, firm recommendations regarding chemotherapy for the mother and prophylactic treatment of the newborn cannot be made. However, the data upon which to base such recommendations may well become available if the incidence of bovine tuberculosis continues to increase throughout the United States.

Summary

In a 28-year-old pregnant woman cavitary pulmonary tuberculosis developed due to Mycobacterium bovis. This is the first report of bovine tuberculosis in pregnancy. The patient responded well to treatment with isoniazid and ethambutol, and, after three months of therapy, delivered a healthy infant. The child received isoniazid chemoprophylaxis.

Six other cases of M bovis infection have been recorded in Los Angeles County in the 30 months between 1974 and mid-1977. Five of them were adults and all had pulmonary involvement. A review of the published experience with bovine tuberculosis in the preceding 20 years in the United States and Canada showed that the disease has, in fact, been seen exclusively in adults and that almost half of them had significant pulmonary findings. Consequently, it is apparent that the age distribution and clinical presentation of the infection has changed dramatically from the era when children were mainly affected and extrapulmonary manifestations of the disease predominated.

It remains to be determined whether the apparent upsurge of bovine tuberculosis in Los Angeles is the result of an increase in imported infection alone or whether it is due in part to growing local consumption of possibly contaminated raw milk.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Marathon Runners With Cardiovascular Disease

To the Editor: A five-year review of the cardiovascular division of the Honolulu marathon shows interesting statistics. The total number of cardiovascular finishers is 81, with a diagnostic breakdown as follows: 34 positive stress test, 30 previous myocardial infarction, 11 post-coronary-bypass surgery, 4 hypertension, 2 congenital heart disease (1 pulmonary valvotomy and 1 ventricular septal defect repair). This group includes 5 women and 76 men with an age range between 25 and 69 years.

Follow-up to date reveals three cardiac events, none related to running. Case 1. A 54-year-old man with a previous myocardial infarction died as a passenger in a plane crash. Case 2. A 54-year-old-man with three-vessel disease died while sleeping, and no autopsy was obtained. Case 3. One nonfatal arrest occurred during sleep in a 51-year-old man with a previous myocardial infarction. Subsequent tests demonstrated hypokalemia which was corrected and he has since resumed training.

We are continuing follow-up on the entire group.

JO ANN SCHROEDER, RN, MS
JOHN O. WAGNER, MD
Education & Research Committee
Honolulu Marathon Association
Honolulu

Exercise and Serum Glutamic Oxaloacetic Transaminase Values

To the Editor: Several surveys have shown that 1 to 4 percent of serum specimens from outpatient populations will show elevated serum glutamic oxaloacetic transaminase (SGOT) values.[1] Causes include diseases involving tissue where this enzyme is stored, such as the liver, heart or muscle; alcohol abuse; congestive heart failure; intramuscular injections, and spurious elevations secondary to drug ingestion.[1]

Therefore, physicians may occasionally see patients with unexplained SGOT elevations, and should remember the effect of *exercise* on transaminase values, especially in our increasingly health-conscious society. Studies involving young, healthy adults exercising for brief periods,[2] or to subjective tiredness,[3] or in vigorous fashion for several days[4] have shown an occasional elevation of the SGOT compared with control values. (The creatine phosphokinase [CPK] levels will rise also.)

An alert physician will not only question patients about their alcohol and drug habits, but also about their recent exercise pattern.

RICHARD R. BABB, MD
Section of Gastroenterology
Palo Alto Medical Clinic
Palo Alto, California

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More on the Prevalence of Amebiasis

To the Editor: In a recent letter Burdick (West J Med 129:77, July, 1978) suggests that amebiasis is an almost vanishingly rare infection in the San Francisco Bay Area. He quotes extremely low detection rates in his and other local hospitals, and cites a report from the Center for Disease Control[1] which indeed deals in part with overdiagnosis of amebic infection, but fails to mention that it also points out instances of underdiagnosis (false negatives).

Neither incidence nor prevalence of amebiasis can be ascertained from figures such as those given by Burdick. The relationship between laboratory diagnosis on clinical specimens and either incidence or prevalence of a disease depends upon a large number of factors including patient

reporting of symptoms, physicians' index of suspicion and utilization of proper laboratory testing, patient compliance in securing tests, and last but not least the competence of the laboratory involved. Parasitologic examinations, unfortunately, are frequently so inadequately performed as to be useless or misleading. The American Society of Parasitologists has recently issued a statement[2] outlining minimal standards for clinical parasitology, both as regards training of personnel and the handling of specimens. Adherence to these standards (or the expanded version which the American Society of Medical Technologists will shortly issue) should result in greatly increased accuracy of diagnosis.

Our laboratory performs stool examinations for a number of the Kaiser hospitals. Records are readily accessible to us for only those patients residing in the Oakland-Berkeley, California, area. For this area, from late 1969 to early 1976, we found 1.7 percent of persons examined to be infected with Entamoeba histolytica. We would not attempt to translate this into a prevalence rate, but suggest that at least in our part of the San Francisco Bay Area amebiasis cannot be considered "extremely uncommon."

In the same period 2.1 percent of patients were found to have Dientamoeba fragilis infections and 4.0 percent giardiasis. In our opinion (shared by Dr. Marietta Voge at the University of California, Los Angeles, and Mr. William Argall of the clinical parasitology laboratory at Stanford [personal communications]) detection of significant numbers of dientamoeba infections is a rough guide to the adequacy of collection and preparation of stool specimens. We would be interested to know how many dientamoeba infections Dr. Burdick's technologists found during the period covered by his report.

EDWARD K. MARKELL, PhD, MD
PATRICIA M. QUINN, BA
RUBY A. KURITSUBO, BS
Departments of Internal Medicine and Clinical Pathology, Kaiser-Permanente Medical Center, Oakland, California

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Refer to: Nelson JH, Stracener CE, Gannon C: Child health assessment and screening using a volunteer staff (In the Forefront). West J Med 129:243-249, Sep 1978

Child Health Assessment and Screening Using a Volunteer Staff

COL JAMES H. NELSON, MC, USA, *Berlin,* COL CARL E. STRACENER, MC(Ret), USA *and* CONSTANCE GANNON, BA, *Tacoma, Washington*

A child health assessment and screening program, staffed by volunteers, has evaluated approximately 5,000 children in a general pediatric clinic. A sample of 500 children was studied to determine characteristics of the population served, quality of the work of the volunteers and the number of new problems identified. Use of well-trained volunteers, provided with adequate supervision and follow-up physicial examination of the children, identified many new problems at minimal cost and proved an effective means of expanding quality health care.

SCREENING FOR common pediatric problems as part of a thorough intake assessment which promotes a child's health support system is widely recommended.[1-4] Preventive pediatrics is the core of quality medical care for children.[5]

This task is most difficult when applied to busy pediatric clinics, charged with the primary care of acute illnesses and limited by time, budget and staff. The general pediatric clinic at Madigan Army Medical Center, Tacoma, Washington, serves a large population (57,392 clinic visits in 1976, excluding well-baby and adolescent clinics). It lacks the primary care staff to offer each child the minimum of preventive care recommended by the American Academy of Pediatrics and other national health organizations.[5,6] To meet this need, volunteers are accepted into the Standard American Red Cross Volunteer Training Courses, following which continuing training is given in pediatric health maintenance and screening techniques. This consists of lectures (12 hours), then observation of complete screening examinations with an experienced screener (two to four weeks) and then actual screening under the direct supervision of an experienced screener for an additional three weeks. After this period, they begin independent screening appointments. Quality control and standardized testing are monitored by an experienced tester who makes unscheduled visits to observe test administration by those who are working independently.

These volunteers, trained in screening techniques by the use of videotapes, in-service lectures, manuals, observation and direct supervision, have assumed a major role in preventive pediatrics. Most of these volunteers are college graduates who are wives of men in the military services; most possess a wide range of backgrounds such as language skills in Korean and Spanish and useful degrees in special education, nursing, psy-

From the Department of Pediatrics, Madigan Army Medical Center, Tacoma, Washington. Dr. Nelson is now Chief, Pediatric Service, Berlin MEDDAC; Dr. Stracener is staff pediatrician, Madigan Army Medical Center, and Clinical Professor of Pediatrics, University of Washington, Seattle; and Ms. Gannon is Educational Specialist and Inservice Education for the Screening Program, Intermediate School District 121, Tacoma.

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The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the view of the Department of the Army or the Department of Defense.

Reprint requests to: Carl E. Stracener, MD, Dept. of Pediatrics, Madigan Army Medical Center, Tacoma, WA 98431.

chology, sociology, speech pathology and occupational therapy. Seniors from local colleges have received college credit while assisting in this program. The typical volunteer schedules four to eight hours each week.

During a three-year period (1975 through 1977), approximately 5,000 children (3 months through 12 years of age) received a 60-minute individual comprehensive health monitoring evaluation given by volunteers. This information was added to the patient's outpatient medical chart, after review of that chart in a problem-oriented form by the volunteers. The completed chart and results of the health monitoring evaluation were reviewed by a pediatrician. This screening information was then available to pediatricians as part of the follow-up 15-minute physical examination scheduled at the time of screening.

The outcome of 500 children seen by the Pediatric Screening Program (PSP) during late 1977 was analyzed for its effectiveness.

Materials and Methods

The 500 children of this study represent consecutive PSP evaluations and are believed to be typical of the overall clinic population. Any child eligible for care at the clinic could be referred for a screening appointment by parents, pediatricians, a nurse or community agencies. Families who had just moved into the area, along with children requiring kindergarten and preschool examinations, were especially encouraged to use this service.

The screening evaluation of the PSP is comprised of five segments:

1. Medical and social histories are compiled in a concise, easily available form to be of immediate value in busy outpatient clinics.

2. Basic standard screening tools are used to detect vision, hearing and speech deficiencies; deviant physical and psychomotor development, and a variety of other problems. The screening tests are requested by the volunteer after consulting standing orders (SOP) which take into account the child's age and major problems. In unusual patients, the volunteer presents the case briefly to a pediatrician who helps decide upon the specific tests to ensure a complete evaluation of identified problem areas. Table 1 shows the screening procedures used in our program and the anticipated prevalence of problems. These screening tests are selected from recommendations of standard sources[7] which have been found to give reproducible results. Great emphasis is made to all concerned that the procedures are only of

TABLE 1.—*Pediatric Screening Procedures (newborns, infants, adolescents not included)*

Prevalence of Abnormalities[7]	*Percent*	*Screening Tools*
Growth	3	Height, weight, head circumference
Vision	6-15	Hirschberg Cover Test, Allen Cards, E Chart, Snellen Chart, color blindness
Hearing	3-5	VASC—pure tone audiometry
Atherosclerosis	2	Serum cholesterol and triglyceride*
Hypertension	1-2	Blood pressure
Tuberculosis	0.2	TB tine, Mono-Vac or Mantoux*
Anemia	1-10	Hematocrit or hemoglobin
Special*	?	*SMA-6, SMA-18, T3 and T4, immunoglobulins, sweat test, blood types, buccal smear, chromosomal analysis, consults, x-rays, UA, alpha-1-antitrypsin, coagulation studies*
Sickle cell	8	Sickle prep or Sickledex*
Immunization lags	40	Check shot records or send to Immunization Clinic
Thalassemia	1-5	Hematocrit, peripheral smear*
Dental	70	Check list, yearly dental check, fluoride prescriptions
G-6-PD deficiency	2-20	Spot test or dye test*
Bacteriuria	2	Urine culture (girls only)
Development	3-10	DDST, Draw-a-Person, QT, Slosson, PPVT
Speech	15	Denver Articulation Screening Test, check list
Behavior	5-50	Sentence completion, check lists, drawings, observation, kinetic family drawing, Burke's Behavior Rating Scale
Specific Learning Disability	3-10	Slosson Drawing Test, handwriting, WRAT, PIAT, Durrell Reading Test Paragraphs, Woodcock Reading
School Readiness	5-10	Memory for Designs Test, MSSST, Spriggle School Readiness Test

DDST = Denver Developmental Screening Test
MSSST = Meeting Street School Screening Test
PIAT = Peabody Intelligence Aptitude Test
PPVT = Peabody Picture Vocabulary Test
QT = Quick Test (Ammon)
SMA = Sequential Multiple Analysis (Technicon)
VASC = Verbal Auditory Screen, Child
WRAT = Wide Range Achievement Test

*High risk populations only.
†Requested by volunteer after consulting standing orders and/or in consort with pediatrician to ensure complete evaluation in unusual patients.

a primary screening nature, and that any new, abnormal or questionable results must be referred to appropriate sources for definitive examination. Only those screening tests deemed applicable are used for any individual child. Definitions of abnormal and normal ranges of results given by each of the listed screening tests are used in this study.

3. Parents are counseled on the use of fluorides, nutrition, poison and accident prevention, and utilization of medical and community resources.

4. A detailed medical chart review is completed. A flow sheet for continued health monitoring and any growth charts required are placed in the record.

5. The pediatrician or nurse clinician selected by the family after discussion with the PSP volunteer sees the child within three weeks and carries out a thorough physical examination. At this time an interpretation of the screening assessment is given to the parents and arrangements are made for any necessary follow-up or consultation.

A 46-question pediatric screening survey (Figure 1) is completed by the parents and volunteer paraprofessionals as part of the initial 60-minute evaluation. Charts are reviewed by the authors several weeks after the physical examination is done to determine the overall effectiveness of the program.

Results

A number of characteristics of the families served by this military pediatric clinic were delineated. The sample indicates that the military family is similar to the local American civilian family in Tacoma[10,11] with a few exceptions. There is no unemployment; the average annual income for an E-4 (lower-ranking enlisted man) is about $8,500 plus extra benefits such as free medical care. Single parent families are rare and few of the mothers work outside the home. A third of the families live in military housing in a somewhat controlled environment. A total of 27 percent of the mothers were born outside the United States with languages other than English used in 17 percent of the homes. Frequent moves and temporary absences of the father from the home remain part of the peacetime military family. Only 28 percent of the families had a specific pediatrician or pediatric nurse clinician until they were given their choice as a result of the screening procedure. The typical child had 8.5 outpatient visits in 3.0 separate outpatient clinics and was seen by 7.6 different professionals during the previous 12 months. The typical child watched 3.6 hours of television a day.

In this sample of 500 families, the typical father was 28.8 years of age and had 14.0 years of education (with 22 percent college graduates). The mothers averaged 26.3 years of age and 13.1 years of education (with 10.7 percent college graduates). Rank of the sponsor was divided among officers (19.3 percent), noncommissioned officers (51.3 percent), and lower ranking enlisted personnel of E-4 and below (29.4 percent). The typical family had 4.3 members, changed homes an average of once a year, and had an absent father for two to four months (32.2 percent), five to seven months (11.6 percent), or eight or more months (13.7 percent) during the past year. Only 19.4 percent of the mothers worked full or part-time outside of the home. Child care for these mothers was provided by a number of various resources including a sitter (not a relative) in another home (36 percent) and a military child care center (15.5 percent).

Figures 2 and 3 indicate that new problems were found, as expected, through the screening. Additional significant problems were found in only 3 percent of the children at the follow-up physical examination.

Review of charts by the authors verified the high quality of work done by the volunteer staff. Growth charts were present in 100 percent of cases, a summary note entered in 92 percent of the cases and health maintenance flow sheets entered in 87 percent of the charts. In 63 percent of the charts all entries were coded out in problem-oriented form. Of the initial screening evaluations, 98 percent were accompanied by the necessary well-child physical examination which is vital for follow-through and quality control.

This survey shows that primary medical care places much greater emphasis on management of acute minor illness and often neglects health maintenance procedures. Therefore, basic screening for anemia, dental care, hypertension, immunization, vision, hearing, growth and development, and the like, has been deficient for many of our pediatric patients. This program has brought improvement.

The following percentages of children had *new* or additional problems detected through the screening procedures: anemia (13 percent), lack of regular dental care (50 percent), lack of daily

Figure 1.—Pediatric Screening Survey.

PEDIATRIC SCREENING SURVEY

INFORMATION REQUIRED BY THE PRIVACY ACT

AUTHORITY:	Sections 133, 1071-87, 3012, 5031 and 8012, title 10, United States Code and Executive Order 9397.
PRINCIPAL PURPOSE:	To obtain needed information about a child's family, support system, and results of data obtained during our pediatric screening program. This is needed to determine if our screening program has been effective, and aid us in improving it.
ROUTINE USES:	It will be used as a source of information, similar to a growth chart or record of immunization by the child' physician. This information will be useful in improving the child's health care by future health professionals.
DISCLOSURE:	Voluntary. Parents do not have to supply information if they do not wish.

QUESTIONS 1-26 TO BE COMPLETED BY PARENTS

1.	Age of child	_____	
2.	Sex of child	Male	Female
3.	Rank of sponsor	_____	
4.	How many biological parents live in the home?	Both Mother only	Father only None
5.	Is the child adopted?	Yes	No
6.	In what branch of service is the sponsor (indicate active or retired)	_____	_____
7.	Age of father	_____	
8.	Age of mother	_____	
9.	How many other children are in the family?	_____	
10.	Is the mother employed outside the home?	Yes, full time Yes, part time	No
11.	If the mother is employed, how is child cared for?	Is not employed Sitter, at home, family Sitter, at home, non-family Sitter, away from home, family Sitter, away from home, non-family Military child care center Other child care center Child attends school	

Continue on next page

PATIENT'S IDENTIFICATION *(For typed or written entries give: Name—last, first, middle; grade; date; hospital or medical facility)*

QUESTIONS 1-26 TO BE COMPLETED BY PARENTS

12.	Type of school child attends	None Pre-school	Kindergarten Grade _____
13.	Since child has been a part of family, family has changed houses	0-2 times 3-4 times	5-6 times more than 6
14.	In the last year, how often has the father been away from home?	0-1 month 2-4 months	5-7 months more than 7 months
15.	Does family live on military installation?	Yes	No
16.	What is the mother's racial/ethnic background? (i.e. German, Korean, etc)	_____	
17.	Is more than one language used in the home?	Yes	No
18.	How much formal education did the mother complete?	_____	
19.	How much formal education did the father complete?	_____	
20.	Has the child had a specific doctor assigned prior to screening?	Yes	No
21.	Have parents sought yearly dental care if child is more than 3 years old?	Child is less than 3 Yes	No
22.	Is child experiencing problems in school?	No Yes, both learning disability and discipline Yes, discipline problems only Yes, learning disability only Other _____	
23.	Is child considered to be a discipline problem at home by parents?	Yes	No
24.	Is child on continual medicine	Yes	No
25.	How many hours a day does child watch T.V.?	_____	
26.	Are shots up to date?	Yes	No

QUESTIONS 27-46 TO BE COMPLETED BY SCREENER

27.	Does patient have chronic problems?	Yes	No	
28.	Was child referred to another clinic or local child related agency as a result of screening?			
29.	Have hearing discrepancies been noted? (can't hear at 20 db either ear - any frequency [1,000 - 4,000 Hc])	Yes	No	NS
30.	If yes, were these detected prior to screening?	Yes	No	
31.	Have visual discrepancies been noted? (20/40 vision or worse or "cross eye" or other)	Yes	No	NS
32.	If yes, were these detected prior to screening?	Yes	No	
33.	Were fluorides started as a result of screen? (if child not drinking on-post water, fluorinate)	Yes	No	NS
*34.	Is height within normal limits?	Yes	No	NS
35.	If no, was abnormality recorded prior to screening?	Yes	No	
*36.	Is weight within normal limits?	Yes	No	NS
37.	If no, was abnormality recorded prior to screening?	Yes	No	
38.	Have speech discrepancies been noted?	Yes	No	NS
39.	If yes, were these detected prior to screening?	Yes	No	
40.	Is head circumference within normal limits? (3 - 97%)	Yes	No	NS
41.	If no, was abnormality recorded prior to screening?	Yes	No	
42.	Is development normal? (M.A./D.A. at least 80% of C.A.)	Yes	No	NS
43.	If no, was abnormality recorded prior to screening?	Yes	No	
**44.	Is blood pressure normal?	Yes	No	NS
45.	If no, was abnormality recorded prior to screening?	Yes	No	
46.	Was Ipecac Rx a result of screen?	Yes	No	NS

Questions 47-52 To Be Completed by Reviewer.

47.	Is Hct normal? (> 32%)	Yes	No	NS
48.	Is UA normal? (no glucose, no protein, greater than trace, no RBC's, no more than 6 WBCs/HPF)	Yes	No	NS
49.	Girls, is urine culture normal? (no growth) (Abnormal: if greater than 100,000 col/ml and organism named)	Yes	No	NS
50.	How many times has patient seen a doctor in the past year?	_____		
51.	In how many locations?	_____		
52.	Number of different doctors seen.	_____		
53.	Other laboratory abnormalities. (Sickle Cell, Alpha-1-antitrypsin, Cholesterol, TB skin test, etc.)	_____ _____ _____		
54.	Other physical abnormalities identified. (caries, dental abnormalities, scoliosis, etc)	_____		
55.	Other social/emotional problems identified	_____		
56.	Was a thorough physical examination done as a separate appointment within six weeks of the screening?	Yes	No	
57.	Does review of chart by reviewer note any problems not followed up by physician at the physical (e.g. UTIs, anemia)?	Yes	No	
58.	Was chart put into problem-oriented form with all entries coded (0, 00, 000, 1,)?	Yes	No	

Height and weight considered "normal" if 10th percentile or greater and if a child's height and weight do not vary more than 30 percentile above. (Example: Wt: 75%, Ht: 50%, normal. Wt: 90%, Ht: 50%, abnormal)

*** A systolic pressure of over 105 or diastolic pressure of over 75 is considered "abnormal" and needs to be double checked against chart for age.*

PATIENT'S IDENTIFICATION *(For typed or written entries give Name—last, first, middle, grade; date, hospital or medical facility)*

fluorides (52 percent), behind in immunizations (19 percent), visual problems (6 percent) and probable hearing loss (4 percent) in addition to other findings noted in Figures 2 and 3.

Discussion

Efforts to promote child health maintenance screening through large scale, organized programs continue to draw much interest,[12,13] support[14,15] and criticism[16-18] in America and other countries.[19,20] The use of skilled volunteers working under the direct supervision of pediatricians with one set of standardized screening tests and tools and using common definitions of normal and abnormal with provision for adequate diagnosis, treatment and follow-up by qualified specialists at little cost to the family and generally part of one health care system is an advantage of this specific program.

Accurate follow-up of all 500 children would be the most valid means of measuring the ultimate value of the screening program. Such follow-up is currently under study by the Early and Periodic Screening, Diagnosis and Treatment (EPSDT) Pilot Programs using outreach case workers (personal communication, R. Curneen, EPSDT Project Director, Tacoma, Washington). In our project, the final outcome was measured in only one area. Of the 500 children, 50 had visual problems noted in screening. Of these, 23 were new cases and the patients were referred to the hospital optometry or ophthalmology clinics. Of these, 20 made and kept appointments. Sixteen were found to have significant refractive

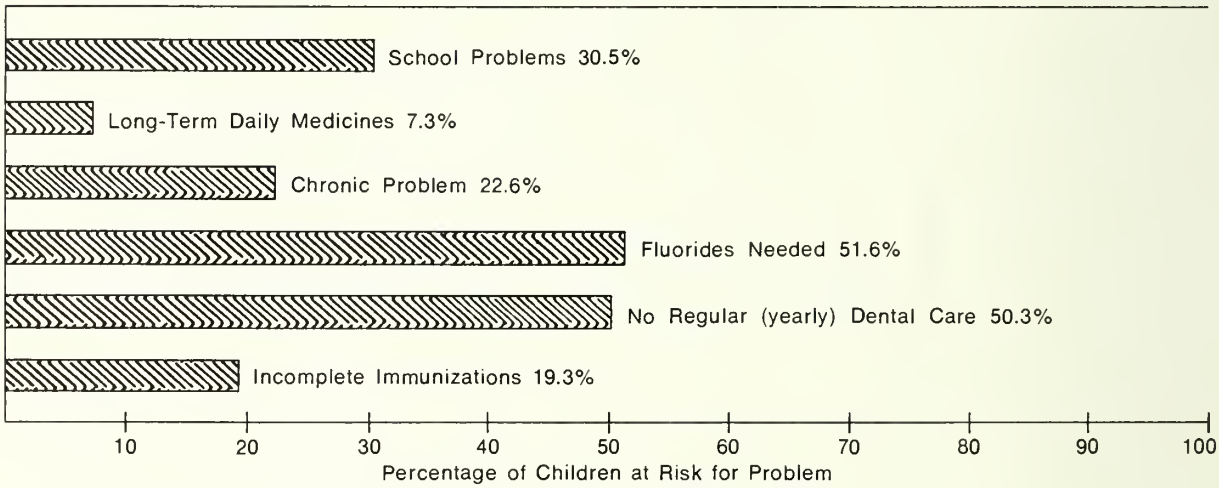

Figure 2.—Problems identified by screening history (sample of 500 families).

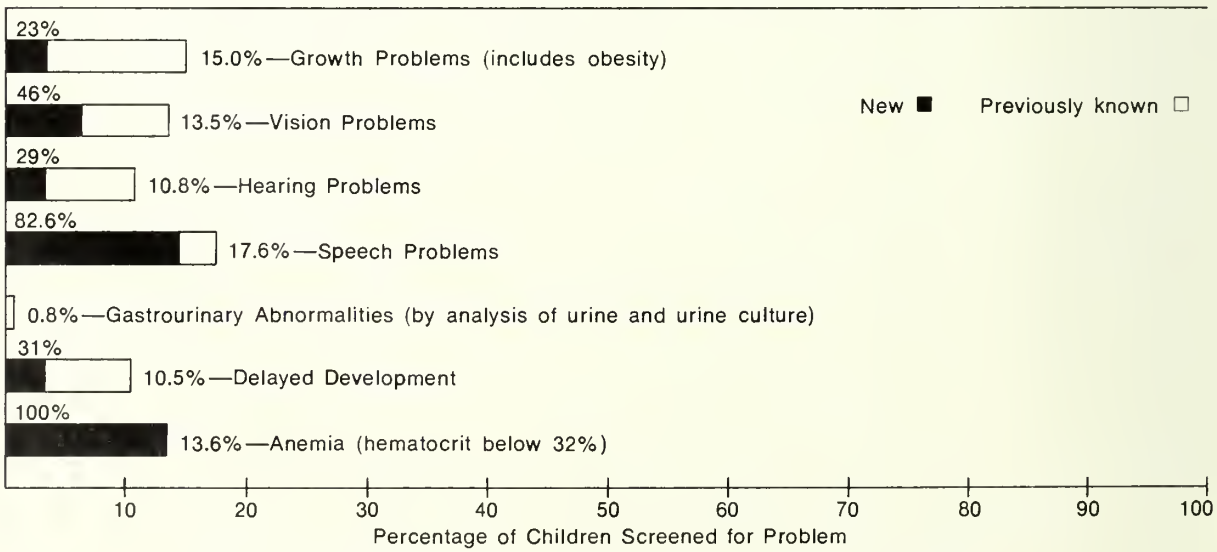

Figure 3.—Problems identified by screening tests (sample of 500 families).

errors. Twelve of the children now have glasses, but only ten of them use the glasses according to telephone reports from the parents.

The value of paraprofessionals and volunteers for routine health screening in a military pediatric clinic was emphasized in a report by Grant and co-workers.[21] This study of 6,058 school age children showed that of the 13.4 percent who had new significant abnormalities detected, three fourths were found by paraprofessional screening and only one fourth were detected by physical examination. The present study which includes more areas of screening, including child development, shows similar results.

The use of paraprofessionals in the screening field has been successfully undertaken by federal agency programs such as EPSDT,[22] a private health care system such as the Kaiser-Permanente Multiphasic Screening Program,[23,24] and certain state agencies.[25] The highly skilled volunteers in this program provide a human, unrushed, caring link and translator between the hurried, concerned physician and the often confused and stressed family.

The volunteers also are valued in teaching the practical aspects of basic screening procedures to medical and nursing students rotating through ambulatory pediatrics. Often, health maintenance interviews are carried out in Korean, Spanish or German, and printed instructions are available in these languages as practical measures to bridge cultural and language barriers.

The large number of American children served by military physicians in the face of a decreased number of primary care physicians[26] emphasizes the need for more physician expanders such as nurse clinicians, physician's assistants and other paraprofessionals.[27] This report documents the value of well-trained volunteers under careful supervision.

While the system has particular application to military pediatric clinics with constant availability of well-educated volunteers who receive free child care services during their work, it again emphasizes the efficacy of paraprofessionals in expanding child health maintenance and screening.

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Refer to: LaDou J: Cumulative injury (Government and Medicine). West J Med 129:250-253, Sep 1978

Cumulative Injury

JOSEPH LaDOU, MD, *Sunnyvale, California*

A few states, notably California, are experiencing large increases in the number and cost of disability settlements under workers' compensation. Claims of cumulative injury for coronary heart disease, hypertension, stroke, cancer and neuropsychiatric problems have all been interpreted as compensable under workers' compensation, even when these conditions are clearly related to the aging process. Legal precedents for such claims are building rapidly throughout the country. The resultant costs may lead to the demise of the workers' compensation system. The situation in California is discussed in detail including the legal aspects, cumulative injury claims by type of disease and age of claimants, legal costs to the individual and the employer, and the economic outlook for the workers' compensation insurance system.

THE CONCEPT of cumulative injury is creating a crisis in the California workers' compensation system. The term "cumulative injury" is legal rather than medical and refers to physical and psychological disabilities that result from repetitive injuries in the workplace. Although these injuries may be minor at the time they occur, over time they can result in medical problems.[1] Cumulative injuries are differentiated from "specific injuries," the latter resulting from one or a series of exposures to toxic substances or traumatic incidents over a short time. Most cumulative injury claims against workers' compensation in the past have been related to disabilities sustained as the result of the physical requirements of work—for example, back problems resulting from years of heavy lifting.

Over the past 15 years, however, a new type of cumulative injury claim has appeared. This type of cumulative injury results from occupational stress rather than from physical work. Such claims are most often for coronary heart disease, hypertension, stroke and other diseases thought to result from emotional stress and tension in the work environment.

These types of claims have become a major source of workers' compensation litigation in California and, to a somewhat lesser degree in Michigan, Minnesota and Wisconsin. In time, it could become a common disability claim in many states since workers' compensation laws in all states recognize cumulative injury to some degree.

The California Experience

California's problems with cumulative injury litigation began with the *Beveridge* decision in 1959, in which the court held that a claimant's back problem resulted from working in a job that aggravated a previously incurred back condition. The decision stated:

> We think the proposition irrefutable that while a succession of slight injuries in the course of employment may not in themselves be disabling, their cumulative effect in work effort may become a destructive force. The fact that a single but slight work strain may not be disabling

From a paper delivered at the California Medical Association Annual Session held in San Francisco, March 19, 1978.

Reprint requests to: Joseph LaDou, MD, Medical Director, Peninsula Industrial Medical Clinic, 1197 East Arques Avenue, Sunnyvale, CA 94086.

TABLE 1.—*State Compensation Insurance Fund—Cumulative Injury Losses, 1969-1976*

Year	Cumulative Injury Losses	Total Incurred Losses	Percent Cumulative Injury
1969 ...	$ 7,325,984	$100,067,523	7.3
1970 ...	8,562,800	103,133,002	8.3
1971 ...	12,116,119	114,642,680	10.6
1972 ...	17,243,135	142,058,617	12.1
1973 ...	20,775,125	161,799,492	12.8
1974 ...	28,831,840	185,882,677	15.5
1975 ...	41,389,290	202,745,027	20.4
1976 ...	45,395,631	209,796,419	21.6

Source: State Compensation Insurance Fund, California.

TABLE 2.—*Industrial Indemnity—Cumulative Injury Losses, 1969-1976*

Year	Cumulative Injury Losses	Total Incurred Losses	Percent Cumulative Injury
1969	$ 589,049	$41,275,773	1.4
1970	857,304	41,554,008	2.1
1971	1,541,399	39,825,806	3.9
1972	1,421,952	49,383,708	2.9
1973	2,625,983	64,071,910	4.1
1974	3,959,237	72,100,139	5.5
1975	5,977,551	67,274,124	8.9
1976	9,885,005	63,082,262	15.7

Source: Industrial Indemnity Company, California.

does not destroy its causative effect, if in combination with other such strains it produces a subsequent disability. The single strand entwined with others, makes up the rope of causation.[2]

The outcome of the *Beveridge* case opened the floodgate to subsequent cumulative injury litigation. Equally important, it established the "date of injury" as the date when the worker becomes aware that his injury is work-related and affects his performance. In effect, the *Beveridge* decision diluted the statute of limitations and thereby allowed compensation for many conditions that stem more from the aging process than they do from occupational stress.

Attorneys, as well as the courts, have also contributed substantially to the problem in California. As Chief Justice Warren Burger has stated, "The harsh truth is that unless we devise substitutes for the courtroom processes, we may be on our way to a society overrun by hoards of lawyers hungry as locusts and brigades of judges in numbers never before contemplated."[3] Few attorneys are unaware of the possibility that at least some of the disability costs of stress-related disease can be apportioned to workers' compensation insurance. Judgments are given more readily and entail awards that grow steadily larger. Case by case, the bulk of precedent established in the courts accumulates.

All workers' compensation claims are financed by a system that includes both private insurance carriers and state workers' compensation insurance funds. Some states, such as California, also permit private employers to be self-insured and government agencies to be legally uninsured. But under each type of arrangement, awards for cumulative injury are becoming an increasing burden to employers, whether they be private or public. The problem stems from three forces: (1) society and government have become increasingly concerned with protecting the health and welfare of the worker, (2) medical and legal practitioners have become more knowledgeable about the physical and psychological effects of occupational stress and (3) workers have become aware of the occupational stress factors in the work environment.

A large number of diseases and physical conditions can be expected to be the subject of workers' compensation claims and litigation. The state of California has already established a precedent for disability awards under workers' compensation for such diseases as myocardial infarction, coronary insufficiency, stroke, diabetes mellitus, cancer, arthritis and allergies, as well as a host of neuropsychiatric problems including alcoholism.

The Economic Impact of Cumulative Injury

Since 1970 in California, the number of cases and dollar amount of individual awards in cumulative injury litigation have spiraled. In just the past three years the number of cases has increased by 33 percent, rising from 8,974 in 1975 to 10,791 in 1976, and to 13,393 in 1977.[4] These figures from the California Workers' Compensation Appeals Board are conservative, but indicate clearly the trend that is occurring. In terms of dollar amounts, total reported losses rose from $18.0 million in 1970 to $137.5 million in 1976, reflecting an increase of 20 percent to 25 percent annually. Although inflation and broader worker coverage and benefits play a part in the increased dollar amounts, the rapid rise in cumulative injury claims as a percentage of all workers' compensation injury claims indicates the seriousness of the problem (see Tables 1 and 2).

Recently published data indicate that during the first two months of 1977 individual compen-

TABLE 3.—*Nature of Principal Injury, 1977 (as Percent of Total Number of Cases)*

Condition	All Disabling Injuries (Percent)	Cumulative Injuries Resolved (Percent)	Cumulative Injuries New (Percent)
Back	24.9	37.7	35.7
Heart/Vascular	7.4	21.1	24.8
Hearing loss	0.2	15.7	15.0
Extremities	54.1	11.5	13.4
Neuroses	n.a.	7.2	4.9
Pulmonary	0.6	1.0	0.9
All others	12.8	5.8	5.3

Source: California Workers' Compensation Institute, September 1977.

TABLE 4.—*Award by Injury, 1977*

Principl Injury	Percent Dollar Loss
Back	32.7
Heart/Vascular	40.8
Hearing loss	6.6
Extremities	7.3
Neuroses	7.0
Pulmonary	1.0
All other	4.6

Source: California Workers' Compensation Institute, September 1977.

TABLE 5.—*Age at Injury (as Percent of Total Cases)*

	All Injuries (Percent)	Cumulative Injuries Resolved (Percent)	Cumulative Injuries New (Percent)
36 years or less	57.4	18.0	16.0
37-51 years	27.1	34.2	35.1
52-60 years	11.7	30.6	33.5
61-65 years	3.0	13.5	11.9
Over 65 years	0.8	3.7	3.5
	(Years)	(Years)	(Years)
Median Age	33.4	51.2	50.7

Source: California Workers' Compensation Institute, September 1977.

sation awards for cumulative injury claims amounted to $9,218 per claimant.[5] This figure is more than 4½ times the amount awarded to individual claimants for specific injury claims. Many cumulative injury claimants also received an additional $7,068 in payment for a specific injury, making a total received of $16,286. In view of this elevated settlement cost and the fact that such claims now account for 10 percent of all compensation claims and are increasing by more than 20 percent annually, the outlook is for ever-higher costs to employers, insurance carriers and society as a whole.

In fact, an insurance industry representative recently warned that, if the number and severity of these cases continue to increase at present rates, workers' compensation could become virtually uninsurable in California.[5] Michigan, Minnesota, and Wisconsin have now begun to entertain cumulative injury disability claims, with early awards that forecast a nationwide cost experience of epidemic proportions.

The number and type of claims in cumulative injury cases provides further insight into the scope of the problem. Back conditions, cardiovascular disease and hearing loss are the most frequent causes, accounting for 37.7 percent, 21.1 percent and 15.7 percent, respectively, of all cumulative injury claims (see Table 3). Each of these conditions also accounts for a higher percentage of claims when compared with disabling specific injuries of these types among the general workforce. Although back problems are the most common cause of cumulative injury claims, cardiovascular conditions are the most costly, amounting to 40.8 percent of all cumulative injury compensation payments (see Table 4). Taken together, back and cardiovascular problems account for almost 75 percent of total dollar awards. These costs clearly indicate the future economic impact of cumulative injury compensation claims.

One major problem related to such claims is that many conditions associated with the normal aging process are included. More than half of the claimants are 50 years of age or older, and more than 15 percent are 60 or older (see Table 5). The age factor suggests that cumulative injury is being used as a source of additional retirement income, at least in a significant number of cases. Furthermore, one study has determined that one of 11 claimants is already retired before claiming compensation.[1] Permanent disability benefits were designed, however, to compensate injured workers for the lack of a competitive advantage in the labor market—not to improve their retirement incomes. Consequently, many argue that benefits to a retired worker would come more suitably from Social Security and other retirement systems.

Essentially all cumulative injury claims are resolved through litigation, and attorneys are retained in 99 percent of the cases. Consequently, as the number of claims increases, the incidence and costs of litigation also increase. From 1974 through 1976 alone, cumulative injury litigation increased by 125 percent. The California experience has been that an active bar is racing far

TABLE 6.—*Average Litigation Expense per Employee*

	Attorney Fees	*Medical-Legal*	*Other*	*Total*
Employee	$ 780	$357	$ 52	$1,189
Employer ...	401	272	88	761
Totals	$1,181	$629	$140	$1,950

Source: California Workers' Compensation Institute, September 1977.

ahead of the insurance industry's ability to control costs, ahead of the medical community's ability to discern true work-related illness and injury, and ahead of the legislature's ability to revise the permanent disability benefit structure to ensure that payments are made only for their intended purpose.

Legal costs for cumulative injury cases are higher than the cost of medical treatment for the injury (see Table 6). For example, a settlement delivering $8,438 in net benefits to an employee costs $1,950 in legal expenses, reflecting an overhead factor of 23 percent.[1] Because court costs and other items funded by taxpayers were not included in these figures, the costs inherent in each litigated cumulative injury settlement may be greatly underestimated.

It is evident that the adversary system for settling cumulative injury claims has subverted the constitutional purpose of the California Workers' Compensation Insurance System. The purpose as stated is "To accomplish substantial justice in all cases expeditiously, inexpensively, and without encumbrance of any character." However, this objective cannot be met under the present court system. It is certainly not possible to settle these claims expeditiously. Fewer than 50 percent of the claims filed with the California Appeals Board are resolved within a year after the filing date, and about 20 percent wait longer than two years. The cost in time and money to employees and employers—not to mention the cost to taxpayers who support the expense of the court—will not decline under the present system of litigation.

It is impossible at present to determine precisely the part that occupational stress plays in the development of any given disease condition. No standard disability formula could ever apply to every specific disease or every group of workers, and development of a settlement system that would apportion costs on a diagnostic basis is highly unlikely. Under such limitations, we can expect that all occupational, stress-related disability claims will be dealt with by an adversary system in which medical experts will be required to determine—and frequently to argue—whether or not a cumulative injury claim against workers' compensation insurance is legitimate. The validity of such a system is questionable, and its cost would be staggering.

Few if any workable solutions have been offered toward containing the runaway costs threatened by cumulative injury litigation. Cumulative injury with its crippling costs, litigious framework, and destructive impact on the workers' compensation system presents a problem that challenges the medical profession to clarify the role of occupational stress in the development of disease.

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Refer to: Roberts NK, Child JS, Cabeen WR Jr: Infective endocarditis and the cardiac conducting system (Clinical Notes in Diagnostic Cardiology). West J Med 129: 254-256, Sep 1978

Infective Endocarditis and the Cardiac Conducting System

NIGEL K. ROBERTS, MD
JOHN S. CHILD, MD
WILLIAM R. CABEEN, JR., MD
Los Angeles

THE PATIENT is a 25-year-old white man. He was the product of a normal pregnancy and achieved his developmental milestones appropriately. When he entered high school, a routine physical examination by the school physician showed an intracardiac murmur. He remembered being seen by another physician but believed that he was normal because he was not restricted in any of his school activities. It happened that three weeks before his admission to the hospital he had been to a dental hygienist.

The patient presented at the emergency room at the University of California, Los Angeles, Medical Center in August 1977 with complaint of weakness and tiredness. It became rapidly apparent that he was acutely ill. He had a temperature of 39°C (102°F). There was evidence of microemboli in that petechial hemorrhages were noted on funduscopic examination, there was a splinter hemorrhage on the nail of his left index finger and a subsequent urine study showed microscopic hematuria. He had a sinus tachycardia of 120 beats per minute and the blood pressure in his right arm was 120/80 mm of mercury. Clinically he was not in cardiac failure although his spleen was palpable. On auscultation he had a normal first and second heart sound, there was a physiologic third heart sound and a grade III/VI ejection systolic murmur down the left sternal border. At the apex there was an ejection click and one observer heard a short early diastolic murmur. His breath sounds were clear with no added sounds. There were no other significant abnormal findings on clinical examination. Laboratory data subsequently showed a hemoglobin value of 12.9 grams per dl, a leukocyte count of 22,000 per cu mm (mostly polymorphonuclear leukocytes) and an erythrocyte sedimentation rate of 72 mm per hour. All six blood cultures later revealed a heavy growth of streptococcus viridans. An electrocardiogram (Figure 1, upper trace) showed sinus rhythm, a normal P-R interval and left anterior hemiblock. No abnormalities were seen on an x-ray film of the chest. An echocardiogram was unremarkable at this time.

The patient was started on a regimen of penicillin, 10 MU, and streptomycin, 1 gram, given intravenously each day. He was placed on total bed rest. Six days after the patient was admitted to hospital an electrocardiogram showed a prolonged P-R interval (Figure 1, lower trace) and the echocardiogram showed early mitral valve closure (Figure 2A) and aortic valve diastolic flutter (Figure 2B), findings both consistent with acute aortic regurgitation. At this time his blood pressure was noted to be 120/10 mm of mercury. Two days later pulmonary edema developed; although treatment was begun with digoxin and diuretics, the patient failed to respond. His blood pressure by now was 120/40 mm of mercury. The following day a Starr-Edwards prosthetic aortic valve replacement was placed in position. At that time a permanent epicardial pacemaking unit was implanted because complete heart block developed during the surgical procedure.

Discussion

Examination of the surgically excised aortic valve not only confirmed that infective endocarditis had partially destroyed the cusps but that the underlying valve was bicuspid. It is now certain that a bicuspid aortic valve is the most common of the congenital cardiac abnormalities[1] and it would have been prudent for the patient to have taken the recommended antibiotic prophylaxis*

From the Division of Cardiology, Departments of Medicine and Pediatrics, University of California, Los Angeles, School of Medicine.

Reprint requests to: Nigel Roberts, MD, Division of Cardiology, Department of Medicine, UCLA School of Medicine, Los Angeles, CA 90024.

*Penicillin G, 1 million units, mixed with procaine penicillin G, 0.6 million units, should be given intramuscularly half an hour to 1½ hours before the operation. Pencillin V, 500 mg, administered orally every six hours should be given for eight doses. For further details consult reference 2.

before dental manipulations.[2] It appeared that as a result of the dental treatment received by the patient, infective endocarditis developed with a streptococcus viridans. Although treatment was instituted the infection seriously damaged the aortic valve and surrounding structures. Behind and to the right of the noncoronary aortic sinus of valsalva lies the atrioventricular node in the right atrium (Figure 3A). Below the noncoronary cusp lies the membranous septum through which the penetrating portion of the bundle travels (Figure 3B). Therefore, both the atrioventricular node and the His bundle are in close proximity to the aortic valve. It was, consequently, not entirely unexpected that infection on the aortic valve led to first degree heart block. A clear correlation has been shown previously both between first degree heart block and noncoronary sinus of valsalva infection and between the development of left bundle branch block and infection burrowing down into the ventricular septum.[3]

The infection eroded the aortic valve to such an extent that the amount of aortic regurgitation that resulted caused elevation of the left ventricular end-diastolic pressure so much as to cause acute pulmonary edema.[4] Failure of medical therapy required the prompt intervention of surgical operation. Although the blood pressure of 120/40

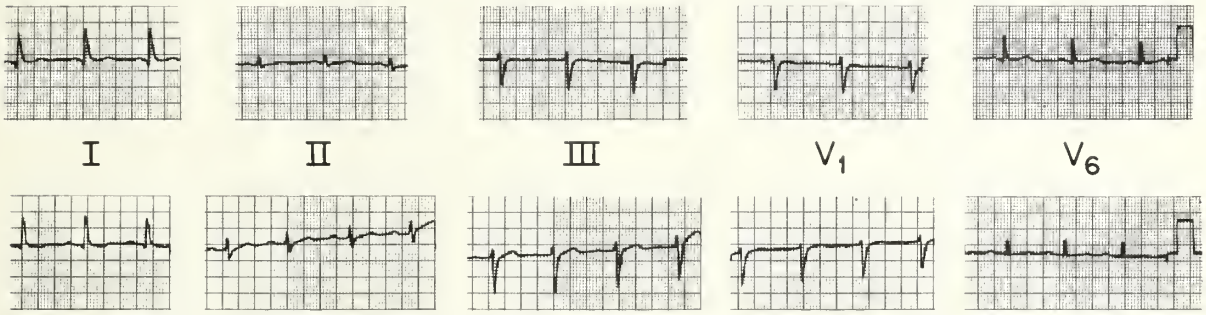

Figure 1.—Upper trace shows standard electrocardiographic leads I, II and III and the precordial leads V1 and V6. At a heart rate of 75 beats per minute the P-R interval is normal at 0.16 second. There is left axis deviation which is consistent with left anterior hemiblock. Lower trace shows electrocardiographic leads comparable to the upper trace but the P-R interval is now 0.24 second, showing first degree complete heart block. There is still left anterior hemiblock.

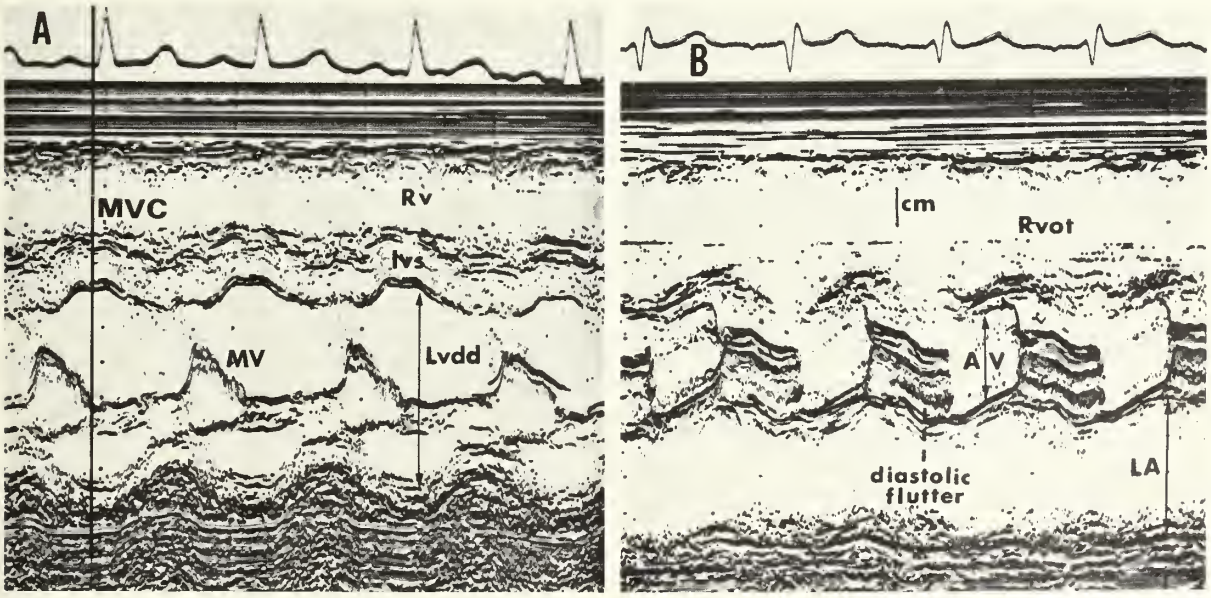

Figure 2.—**A,** M mode echocardiogram showing premature mitral valve closure (MVC). Normally the MVC occurs 0.04 to 0.07 second after the onset of the QRS. Flutter of the anterior mitral leaflet (MV) is seen, consistent with aortic insufficiency (AI). However, premature MVC suggests acute severe AI. Lvdd = left ventricular diastolic dimension; MV = mitral valve; MVC = MV closure; RV = right ventricle. **B,** Aortic valve echocardiogram. The thick diastolic closure line of the aortic valve (AV), with diastolic flutter, suggests a flail aortic leaflet. It is evident that the AV otherwise has normal systolic excursion and thin AV leaflets, and is against a thickened and stenotic valve. cm = centimeter calibration; LA = left atrium; RVOT = right ventricular outflow tract.

mm of mercury appeared satisfactory it was misleading because pressures of 120/10 mm of mercury previously recorded. The increase in diastolic pressure in this situation merely represented the rising left ventricular end-diastolic pressure. Although technically the operation was a success during the time in the operating room complete heart block developed. This may have been due to surgical trauma; however, because of previous evidence of conducting system damage by the disease process it seemed likely that in our patient the complete heart block was a result of this disease process.

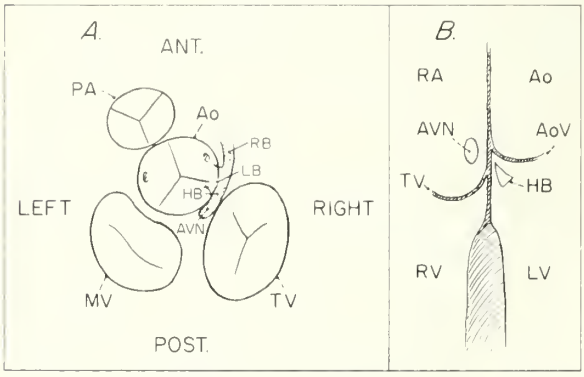

Figure 3.—A, Transverse section of the heart showing in diagramatic form the relationship of the pulmonary artery (PA) to aorta (Ao). The mitral valve (MV) and tricuspid valve (TV) lie posterior to the Ao. The atrioventricular node (AVN) lies in the right atrium in close proximity to the septal leaflet of the TV. The His bundle (HB) lies below the noncoronary cusp of the aortic valve (AoV), and the conducting system continues as the right bundle (RB) after the left branches (LB) have entered the septum. **B,** A longitudinal cut through the right atrium (RA) and Ao showing the relationship of the AVN and HB to the AoV.

In summary, our patient was found to have conducting system involvement during the course of infective endocarditis. This involvement was accompanied by severe valve damage which subsequently caused cardiac decompensation that did not respond to medical therapy.

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4. Morganroth J, Perloff JK, Zeldis SM, et al: Acute severe aortic regurgitation—Pathophysiology, clinical recognition and management. Ann Intern Med 84:223-232, 1977

Antacid-Induced Hypermagnesemia

THE COMMONEST CAUSE of hypermagnesemia may be magnesium-containing antacid therapy . . . We have been cognizant of the problem of inadvertently continuing antacid therapy at a time that renal insufficiency has supervened. I should also point out that even in the absence of renal insufficiency, there have been cases reported of accidental overdosage of magnesium-containing purgatives and this has resulted in significant hypermagnesemia. Again to emphasize the point, in our opinion hypermagnesemia is commonly encountered in patients receiving antacid therapy with magnesium-containing antacids, and that usually there is a degree of renal impairment that is also playing a role in the case.

—ROBERT WHANG, MD, *Indianapolis*

Extracted from *Audio-Digest Internal Medicine,* Volume 25, Number 6, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1577 E. Chevy Chase Drive, Glendale, CA 91206.

ARTICLES TO READ IN OTHER JOURNALS

EDITOR'S NOTE: *Members of the Editorial Board on occasion call attention to articles that they consider to be important in other journals. The editors believe that these titles together with a brief assessment of the articles are worth publishing for the information of our readers.*

Laminaria as an Adjunctive in Induction of Labor

Cross WG, Pitkin RM

Obstetrics and Gynecology
51:606-608, May 1978

DISCIPLINES: General Practice, Obstetrics, Gynecology

READABILITY: Very good

This careful study done at the University of Iowa Medical School could have considerable practical value, especially in obstetrical patients who are candidates for induction but have unfavorable cervices. The placement of three to five laminarias in the cervical os approximately 15 hours before amniotomy shortened the delivery time by about three hours, without complication.

—E. R. W. FOX, MD
Coeur d'Alene, ID

Sonography of the Common Bile Duct: Value of the Right Anterior Oblique View

Behan M, Kazam E

American Journal of Roentgenology
130:701-709, Apr 1978

DISCIPLINES: Internal Medicine, Surgery, Radiology

READABILITY: Good

This article not only introduces a useful new view for depiction of the common bile duct, but serves to illustrate the exquisite anatomic detail available with modern ultrasound techniques. The authors report an over-all accuracy of 96 percent and visualize common ducts as small as 3 mm in diameter.

—ROBERT B. ENGLE, MD
Laguna Beach, CA

Maternal and Fetal Outcome of Lamaze Prepared Patients

Hughey MJ, McElin TW, Young T

Obstetrics and Gynecology
51:643-647, Jun 1978

DISCIPLINES: Family Practice, Nursing, Obstetrics and Gynecology

READABILITY: Good

This controlled study of 1,000 consecutive obstetrical deliveries done at Northwestern University Medical School showed that in the Lamaze prepared patients there were a quarter the number of cesarean sections, one fifth the incidence of fetal distress, a third the number of infections, and fewer perineal lacerations.

In the controls there were three times as many toxemias, and twice as many premature infants. The authors imply, however, that judicious use of episiotomies and outlet forceps might protect the infant's calvarium and its contents, and prevent future perineal relaxation.

—E. R. W. FOX, MD
Coeur d'Alene, ID

Neurofibromatosis in Children

Holt J

American Journal of Roentgenology
130:615-639, Apr 1978

DISCIPLINES: Pediatrics, Internal Medicine, Neurology, Orthopedics, Radiology

READABILITY: Excellent

The bizarre and protean features of this often "devastating, destructive, and debilitating" disease are well covered in this excellent review. The author points out that neurofibromatosis is as common as cystic fibrosis or Down disease. He pleads that more attention be directed to this important crippling illness. A variety of illustrations show the diverse organ involvement and complications which may be seen.

—ROBERT B. ENGLE, MD
Laguna Beach, CA

Prophylactic Use of Cefazolin in Monitored Obstetric Patient Undergoing Cesarean Section

Wong R, Gee CL, Ledger WJ

Obstetrics and Gynecology
51:407-410, Apr 1978

DISCIPLINES: General Practice, General Surgery, Gynecology, Obstetrics

READABILITY: Very good

Dr. Ledger and his group have done another careful study of the perioperative use of antibiotics. They conclude that a short, three-dose course of cefazolin in high-risk cesarean section patients will lower the incidence of postoperative endomyometritis. However, no benefit accrues from the routine use in low-risk patients.

—E. R. W. FOX, MD
Coeur d'Alene, ID

Retropharyngeal Tendinitis

Haun C

American Journal of Roentgenology
130:1137-1140, Jun 1978

DISCIPLINES: Internal Medicine, Orthopedics, Neurology and Neurosurgery, Radiology

READABILITY: Very good

Acute neck pain, aggravated by swallowing or moving the head, heralds the onset of this self-limited disease. The diagnosis is based on calcification and soft tissue swelling in the retropharyngeal area anterior to the clavicle as seen on a lateral radiograph of the cervical spine. This little-known disease is probably not uncommon. Its early recognition permits reassurance of the patient and avoids extensive further workup.

—ROBERT B. ENGLE, MD
Laguna Beach, CA

BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

THE NEUROPSYCHOPATHOLOGY OF WRITTEN LANGUAGE—Joseph H. Rosenthal, MD, Director, Learning Disabilities Clinic, Department of Pediatrics, Kaiser-Permanente Medical Center, Oakland; Assistant Clinical Professor, Department of Psychiatry, University of California, San Francisco. Nelson-Hall Inc., Publishers, 325 W. Jackson Blvd., Chicago, IL (60606), 1977. 168 pages, $12.95.

The physician who finds himself increasingly interested and involved in the sometimes unsatisfactory school and preschool learning experiences of his young patients will find that Dr. Rosenthal has reviewed, digested and evaluated an immense amount of the literature and research on language development. It is not a how-to-do-it book, but Dr. Rosenthal is a pediatrician who believes that the starting point is a careful history (including believing a parent who thinks something is wrong) and physical examination.

The extensions of that history and physical examination that make them meaningful for the child with language problems are clarified and put into perspective, though not detailed, and the background material that other disciplines working in the fields of learning and language work from is presented and their language decoded.

The development of language, including not only early man but other species (even bees do it), is presented and its importance to developing infants and children discussed. The relationship of language to mastery of self and environment, and the devastating effects that cognitive and sensory deficits have in early life are appropriately emphasized.

Pertinent reviews of known genetics, neurophysiology, learning theories, and clinical and anecdotal material are presented, some in detail that will be of more interest to the specializing student than to the clinician.

There are useful reviews of what little is known about some of the nontraditional approaches that keep popping up, and that lay people seem to know more about and have more faith in than physicians. The latter tend to like to know what they are doing before they do it, even when it seems to help.

Recent law mandates education for all of the handicapped. It is essential that physicians be informed child advocates who can monitor their patients and families through the increasing involvement with the educational establishment and the learning and language specialists who are the guardians of the resources that evaluate and remediate many of the handicaps. Dr. Rosenthal's book will be a useful addition to the library of the physician who wishes to understand in depth the language handicapped child, whether seriously impaired or a "slow learner," and a "must" for the serious student.

HENRY S. RICHANBACH, MD
Burlingame, California
Assistant Clinical Professor and Consultant to Learning Problems Clinic, Stanford University

* * *

SKIN SURGERY—Fourth Edition—Edited by Ervin Epstein, MD, Associate Clinical Professor of Dermatology, University of California, San Francisco; Chief of Dermatology and Syphilology at Highland-Alameda County Hospital, Oakland; Consultant to Oakland Area Veterans' Hospital; and Ervin Epstein, Jr., MD, Assistant Clinical Professor of Dermatology, Assistant Research Dermatologist, University of California, San Francisco; Consultant to Oakland Area Veterans' Hospital. Charles C Thomas, Publisher, 301-327 East Lawrence Ave., Springfield, IL, (62717), 1976. 839 pages, $98.75.

The fourth edition of *Skin Surgery* is an expanded and generally upgraded version of the 1970 third edition. It represents the combined effort of 43 contributors and the editors, encompassing 51 chapters. It is multidisciplinary in its approach; it represents the input of authorities not only in dermatology and plastic surgery, but also in a variety of surgical specialties.

The editors have held rather loose reins over the contributors with resultant advantages and disadvantages. An advantage is that each chapter is written in an independent manner by an acknowledged author in his field of expertise. As might be expected, there is some overlapping of subject material by the writers of different disciplines. This is not necessarily a disadvantage, for it provides the reader with more than one point of view, more than one approach, to the same problem.

A greater degree of editorial control over the nature and quantity of the contents might have been an asset. Starting with "Max the Knife," a poem of questionable taste for the stature of this book, and ending with "Do It Yourself" Instruments, such as measuring spoons and cake decorators, some editorial surgery was in order. In particular, the chapters on maxillofacial prosthetics, perfusion techniques, and extensive surgical procedures of male genitalia, are not in the scope of practicing dermatologists. "Surgical alternatives" such as therapy with x-ray, 5-fluorouracil, and topical nitrogen mustard were given appropriate short shrift, treatment that similarly should have been given to immunotherapy and topical cytotoxic therapy. "Superficial chemosurgery" was summarized in 60 pages and probably could have been condensed. The whole chemosurgical terminological conundrum is perpetuated herein and needs final resolution.

The quality of the book as regards the binding, readability of the print and pictures (with some exceptions) is good.

Despite the relatively limited adverse criticisms, *Skin Surgery* clearly stands alone as *the* reference book for anyone with an interest in cutaneous surgery. I believe that it belongs in the personal library of all dermatologists, in practice or in training. No one dermatologist will agree with all of its approaches, but as a "shotgun" approach it provides something for everyone.

JOHN R. STEVENSON, MD
San Diego

* * *

ANGINA PECTORIS—Edited by Desmond G. Julian, MD, FRCP, British Heart Foundation Professor of Cardiology, University of Newcastle upon Tyne. Churchill Livingstone—Medical Division of Longman Inc., 19 West 44th St., New York City (10036), 1977. 272 pages, $25.00.

Among recently published books, multiauthored monographs dealing with a single disease or subject occupy a prominent place. This is to some extent due to the fact that so many postgraduate programs are being taped and edited for publication. Consequently, such a popular and controversial subject as coronary artery disease has been amply covered in the past few years.

This monograph was published in England, under the editorship of a well-known student of ischemic heart disease. It consists of 13 chapters, five of which are written by American authors, one by a Swedish author and the remainder by authors from the British Isles—with a heavy contribution from Scotland. The arrangement of the book is conventional. The first chapter provides an historical introduction by M. B. Matthews, which is interesting in that it includes some details of early recog-

nition of coronary artery disease, which are not generally known. Epidemiology is dealt with by M. F. Oliver. Pathological features of angina are presented by W. C. Roberts. The chapter on clinical diagnosis (M. B. Matthews) is very well written, with considerable detail given to the presentation of varieties of chest pain, the influence of various factors upon pain and the differentiation of anginal pain from other forms of pain. The chapter on physical examination, written by J. K. Perloff, is presented with the usual clarity. E. Varnauskas reviews exercise testing comprehensively and well. The following chapters include discussions of myocardial perfusion (Resnikov), hemodynamics (Friesinger) and angiocardiography (Griffiith and Aschuff). Treatment is covered by Lorimer (medical therapy) and by Balcon, Caves and Stinson (surgical therapy).

In a subject as widely covered by books, monographs and review articles as is angina pectoris it is difficult to find anything presenting new approaches or information. This book presents a collection of well-written articles by well-chosen essayists. The approach is clinical with emphasis on practical aspects of coronary disease and with avoidance of controversial aspects. The volume is attractively printed and well illustrated. The bibliography is adequate without being encyclopedic. It is altogether a useful book for practicing physicians, more a practical guideline than a reference volume.

ARTHUR SELZER, MD
Chief of Cardiology
Pacific Medical Center
San Francisco

* * *

PIAGETIAN THEORY AND ITS IMPLICATIONS FOR THE HELPING PROFESSIONS: Emphasis—The Handicapped Child—Proceedings Sixth Interdisciplinary Conference: Co-sponsored by University Affiliated Program, Childrens Hospital of Los Angeles and the University of Southern California School of Education. USC Special Order Department & Bookstore, University of Southern California University Park, Los Angeles (90007), 1977. 462 pages, $10.00 (Paperback).

Piagetian concepts and strategies are enjoying widespread adaptation as tools for cognitive development and enhancement and, therefore, this volume is a timely contribution.

The first portion of this volume deals specifically with handicapped children. Reports of the effects of piagetian strategies with groups such as mentally retarded persons and visually handicapped learners (Swallow) and emotionally disturbed children (Lubin) are included along with the results of piagetian-based cognitive assessment with young exceptional children (Poulsen) and young disturbed children (Delany, Fitzpatrich).

The remainder of the proceedings, though eluding categorical definition, cover a wide assortment of piagetian related topics. For example, the four stages of cognitive development as given by Piaget—sensory motor, preoperational, concrete and formal operations—are examined.

Notwithstanding, it should be pointed out that not all contributors uniformly endorse the use of piagetian-constructs as models for curriculum development. Interestingly, Gaudia notes that "less than one tenth of 1 percent of Piaget's enormous literary outpourings even deal with the topic of education." Piaget's predominant involvement has traditionally resided in the philosophic realm of genetic epistomology. Murray cautions that "the only possible education recommendation from a theory such as Piaget's is that schools should simulate 'natural' human development" and "should not ignore the theoretical ambiguities."

Therefore, the topics of some sixty papers amassed here extend from investigative research with diverse populations of children, to projects comparing the cognitive development of normal and exceptional groups of pupils using piagetian-based criterion measures. Such a heroic collection supplies as stunning a store of information on the subject as is probably available under one cover. However, the sheer quantity of material is (paradoxically) at once its major flaw. The articles appear as a random compilation rather than a systematic arrangement based on predetermined categories.

Finally, the book concludes with a comprehensive list of references and citations gathered from all the papers. Such an impressive listing provides the reader with an extraordinary and rich supply of resource material.

Some thoughtful editing would not only have eliminated the few weaknesses, but would have added to the clarity and thrust of the entire collection. The articles represent a broad cross section of educational and psychoeducational disciplines and furnish a multifaceted prospective of piagetian theory and implications.

CYNTHIA F. BERROL, PhD
California State University
Hayward, California

* * *

ARGON LASER PHOTOCOAGULATION—H. Christian Zweng, MD, Palo Alto Retinal Medical Group, Inc.; Clinical Professor of Surgery (Ophthalmology), Stanford University School of Medicine; Hunter L. Little, MD, Palo Alto Retinal Medical Group, Inc.; Associate Clinical Professor of Surgery (Ophthalmology), Stanford University School of Medicine; in collaboration with Arthur Vassiliadis, PhD, Staff Scientist, Palo Alto Retinal Research Foundation, Menlo Park, California. The C. V. Mosby Company, Publishers, 3301 Washington Blvd., St. Louis (63103), 1977. 319 pages, $42.50.

This 319-page book describes the indications, contraindications, and complications of argon laser photocoagulation.

The text is well-written and is accompanied by illustrations which are good to excellent. A conversational and clinically oriented tone is maintained throughout the extensive review of the authors' experience during 11 years of argon laser work.

The book begins with a definition of light and lasers, proceeds to photocoagulation effects upon retinal histology in health and disease, and then describes in detail suggested routines for treatment of the various types of retinal degenerative, inflammatory, and vasculoproliferative pathology.

The history of laser retinal photocoagulation has been one of controversy. The idea of producing destructive lesions as a form of beneficial therapy seemed at first to be contradictory. Particularly for degenerative diseases which tend to progress irrespective of treatment, decisions to treat rather than to observe demand that a degree of retardation or stabilization of disease rather than improvement must be accepted as successful therapy. Authors Zweng, Little and Vassiliadis are innovators, and introduced argon slit lamp photocoagulation to the ophthalmologic community in 1966. They have been active proponents of argon laser therapy. Their clinical experience has been extensive and they have documented their results well. Importantly, the authors emphasize that proper utilization of argon laser photocoagulation is not without hazard and that complications must be avoided by more clearly defined indications and contraindications to treatment.

This book is intended for clinicians and is very useful. It presents a balanced viewpoint on a number of controversial subjects. It is regrettable that the senior author (Zweng) died last year, for he contributed greatly to the implementation of argon laser therapy in clinical ophthalmology.

ROBERT E. CHRISTENSEN, MD
Professor of Ophthalmology
UCLA School of Medicine
Los Angeles

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HISHAM TAMIMI, MD, Seattle
Assistant Professor
Department of Obstetrics-Gynecology
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- **Diagnosis and Management of Endometrial Carcinoma**
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Senior Psychiatrist
The Menninger Foundation

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A complete copy of the scientific program is available from: **WSMA Convention Manager, 900 United Airlines Building, 2033 Sixth Avenue, Seattle, Washington 98121, (206) 623-4801.**

in memoriam

Baldigo, Edward Michael, Santa Rosa. Died June 29, 1978 in Santa Rosa of arteriosclerosis, aged 63. Graduate of the University of Minnesota Medical School, Minneapolis, 1940. Licensed in California in 1950. Dr. Baldigo was a retired member of the Sonoma County Medical Association.

Blanchard, Leland B., San Jose. Died June 28, 1978 in San Jose of heart disease, aged 66. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1937. Licensed in California in 1937. Dr. Blanchard was a member of the Santa Clara County Medical Society.

Cook, Robert Arthur, Ukiah. Died July 4, 1978 in Ukiah of heart disease, aged 43. Graduate of Indiana University School of Medicine, Bloomington-Indianapolis, 1960. Licensed in California in 1969. Dr. Cook was a member of the Mendocino-Lake County Medical Society.

Craig, Charles A., Lakeport. Died July 2, 1978 in Lakeport, aged 85. Graduate of the University of California Medical School, Berkeley-San Francisco, 1917. Licensed in California in 1917. Dr. Craig was a retired member of the Mendocino-Lake County Medical Society.

Curtis, Claude C., Bishop. Died March 2, 1978, aged 63. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1940. Licensed in California in 1946. Dr. Curtis was a member of the Inyo-Mono County Medical Society.

DeVoe, Robert W., San Leandro. Died June 24, 1978 in San Leandro of diabetes, aged 64. Graduate of the Creighton University School of Medicine, Omaha, 1943. Licensed in California in 1944. Dr. DeVoe was a member of the Alameda-Contra Costa Medical Association.

Duncan, Herbert A., Pasadena. Died June 3, 1978, aged 69. Graduate of Western Reserve University School of Medicine, Cleveland, 1936. Licensed in California in 1938. Dr. Duncan was a member of the Los Angeles County Medical Association.

Ermshar, Herman F., Fullerton. Died June 24, 1978 in Fullerton, aged 73. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1931. Licensed in California in 1947. Dr. Ermshar was a member of the Orange County Medical Association.

Gang, Michael Jay, Escondido. Died July 7, 1978 in Escondido, aged 39. Graduate of New York University School of Medicine, New York, 1963. Licensed in California in 1968. Dr. Gang was a member of the San Diego County Medical Society.

Haines, Charles Leroy, sr., Died July 9, 1978, aged 89. Graduate of Jefferson Medical College of Thomas Jefferson University, Philadelphia, 1914. Licensed in California in 1926. Dr. Haines was a member of the Los Angeles County Medical Association.

Harmon, Thelma G., San Francisco. Died May 2, 1978, aged 74. Graduate of the University of California Medical School, Berkeley-San Francisco, 1931. Licensed in California in 1931. Dr. Harmon was a member of the San Francisco Medical Society.

Kelly, Hobart M., Riverside. Died June 8, 1978 in San Diego, aged 74. Graduate of the University of Wisconsin Medical School, Madison, 1932. Licensed in California in 1938. Dr. Kelly was a retired member of the Riverside County Medical Association.

Lindenauer, David T., Hollywood. Died April 15, 1978 in Oxnard of arteriosclerosis, aged 78. Graduate of New York University College of Medicine, New York, 1925. Licensed in California in 1941. Dr. Lindenauer was a member of the Los Angeles County Medical Association.

Patton, Edwin F., Los Angeles. Died June 4, 1978, aged 82. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1921. Licensed in California in 1922. Dr. Patton was a member of the Los Angeles County Medical Association.

Rector, John M., San Francisco. Died July 11, 1978 in Nevada City, aged 74. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1930. Licensed in California in 1934. Dr. Rector was a retired member of the San Francisco Medical Society.

Sadusk, Joseph Francis, jr., Oakland. Died July 3, 1978 in Walnut Creek of bronchopneumonia, aged 68. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1935. Licensed in California in 1946. Dr. Sadusk was a member of the Alameda-Contra Costa Medical Association.

Testa, Fillmore, Los Angeles. Died May 28, 1978 in Glendale, aged 74. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1933. Licensed in California in 1933. MD degree from California College of Medicine, 1962. Dr. Testa was a member of the Los Angeles County Medical Association.

Wang, Carl C., Fresno. Died July 16, 1978 in Fresno, aged 80. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1937. Licensed in California in 1937. Dr. Wang was a retired member of the Fresno-Madera Medical Society.

Wohlgemuth, Richard, Glendale. Was killed June 18, 1978 in a hang glider accident at Lake Mead, Nevada, aged 53. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1953. Licensed in California in 1954. Dr. Wohlgemuth was a member of the Los Angeles County Medical Association.

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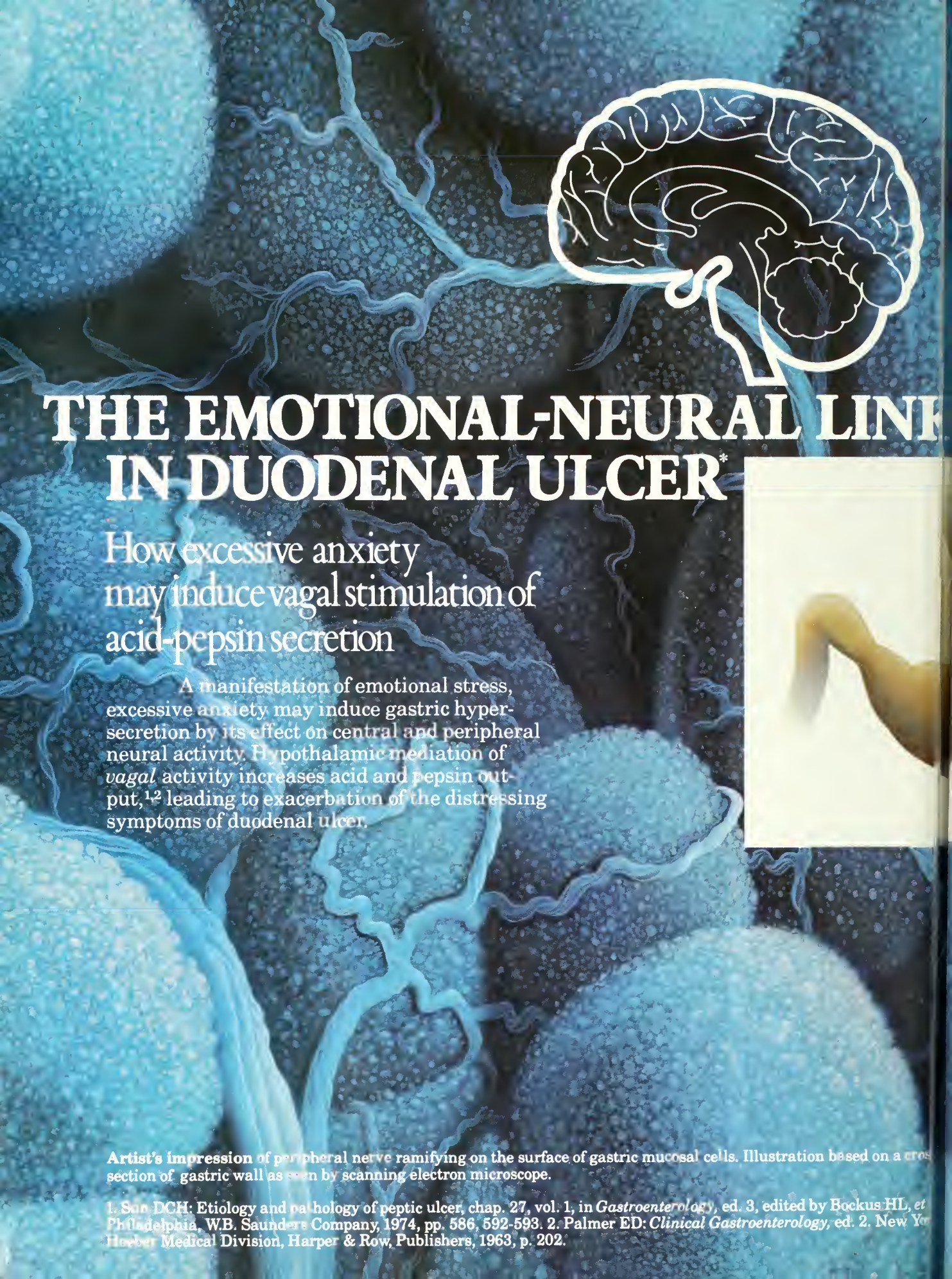

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Artist's impression of peripheral nerve ramifying on the surface of gastric mucosal cells. Illustration based on a cross section of gastric wall as seen by scanning electron microscope.

1. Sun DCH: Etiology and pathology of peptic ulcer, chap. 27, vol. 1, in *Gastroenterology*, ed. 3, edited by Bockus HL, *et al*. Philadelphia, W.B. Saunders Company, 1974, pp. 586, 592-593. 2. Palmer ED: *Clinical Gastroenterology*, ed. 2. New York, Hoeber Medical Division, Harper & Row, Publishers, 1963, p. 202.

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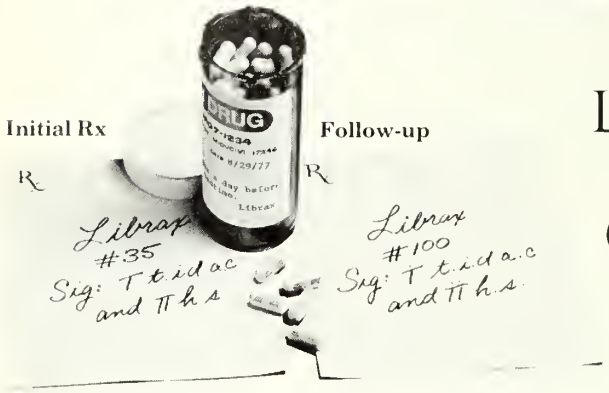

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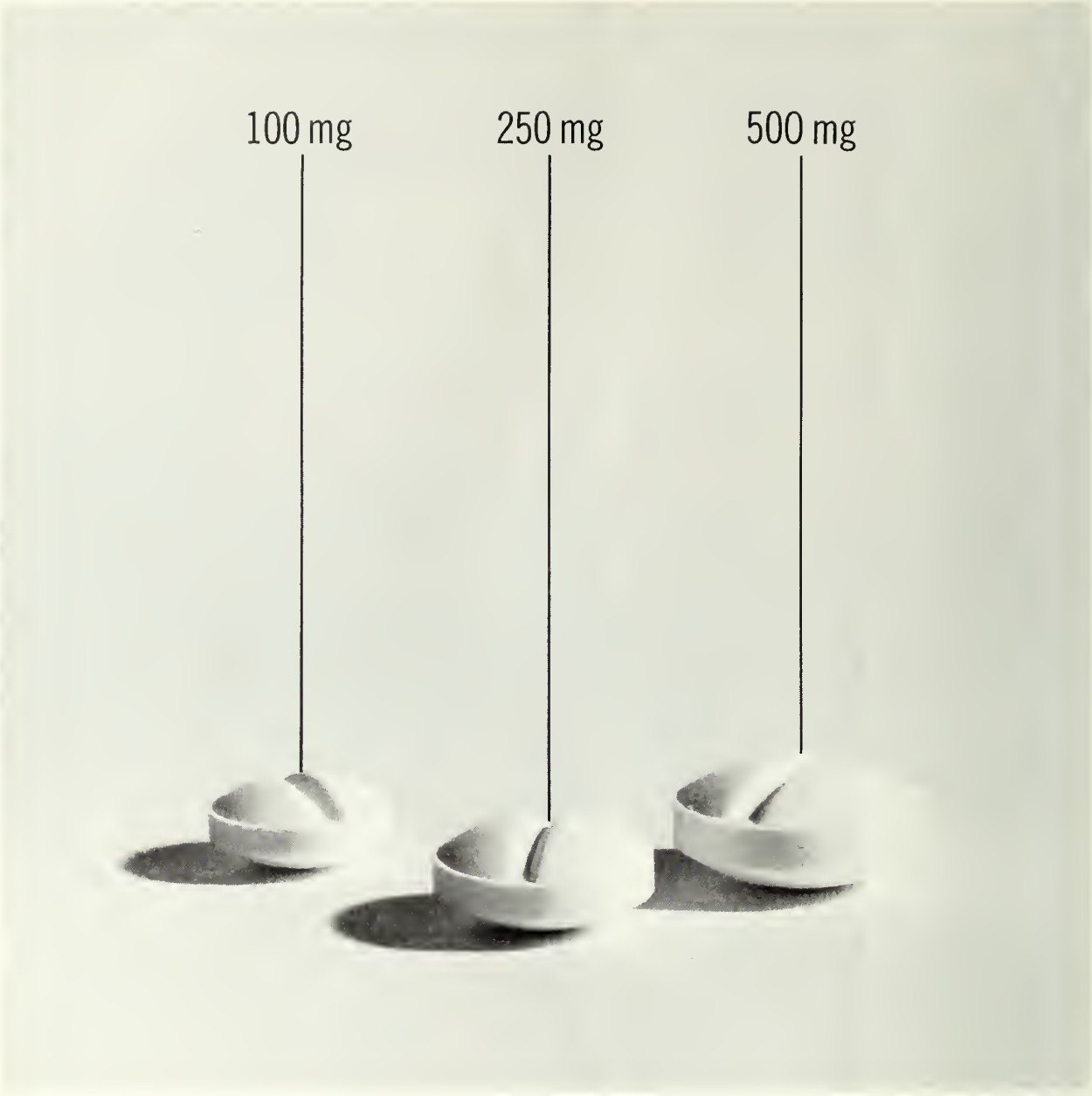

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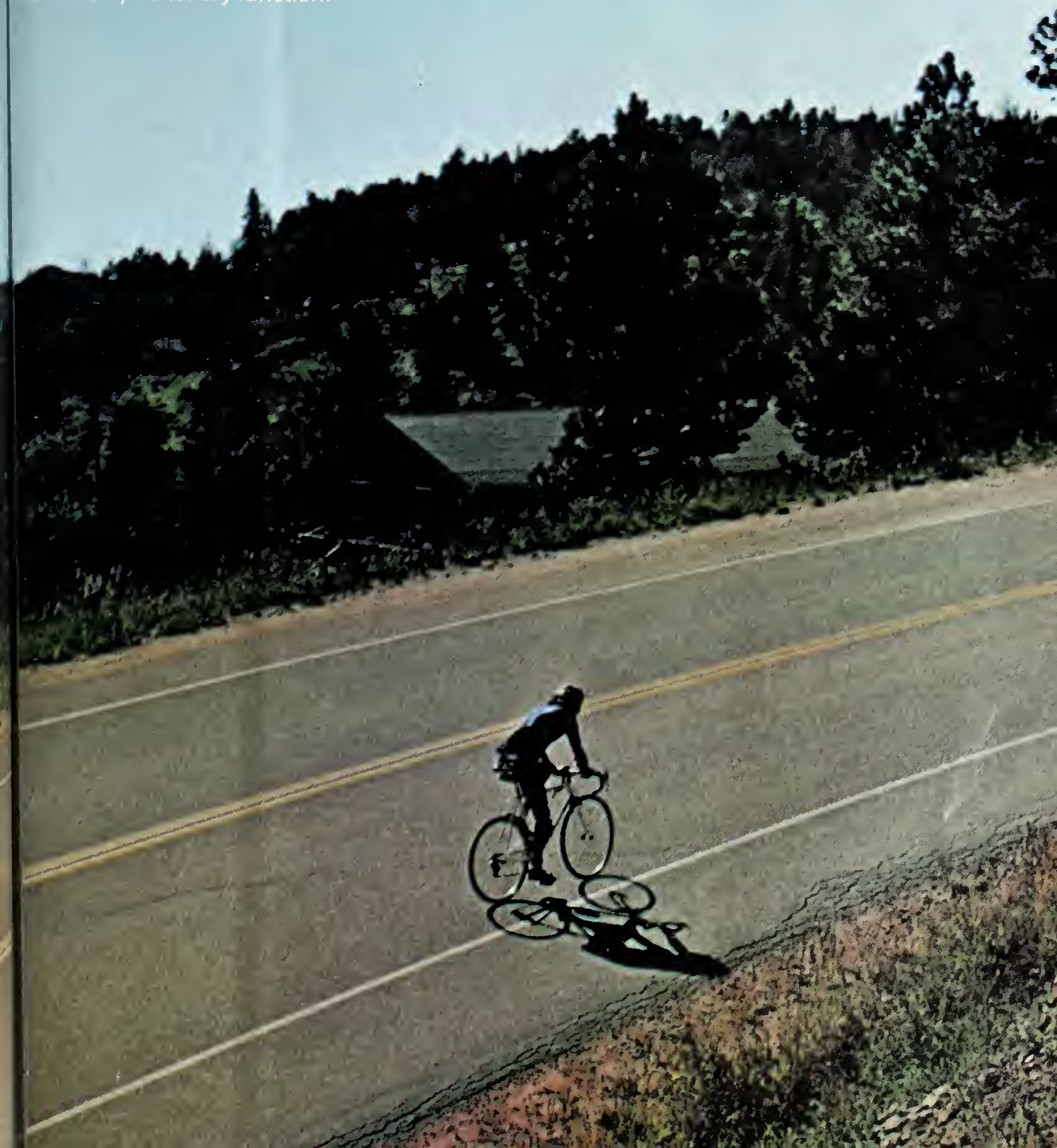

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1. Formgren H: The therapeutic value of oral long-term treatment with terbutaline in asthma. Scand J Respir Dis *56*(6):321-328, 1975.
2. Larsson S et al: Lack of bronchial beta adrenoceptor resistance in asthmatics during long-term treatment with terbutaline. J Allergy Clin Immunol *59*(2):93-100, 1977.
3. Wilson AF et al: Cardiopulmonary effects of long-term bronchodilator administration. J Allergy Clin Immunol *58*(1):204-212, 1976.

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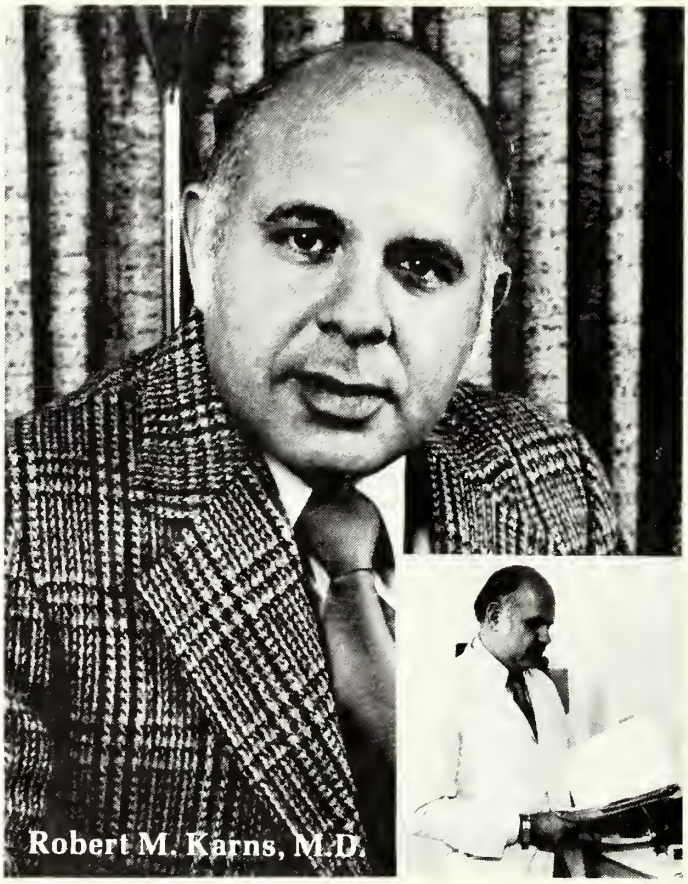

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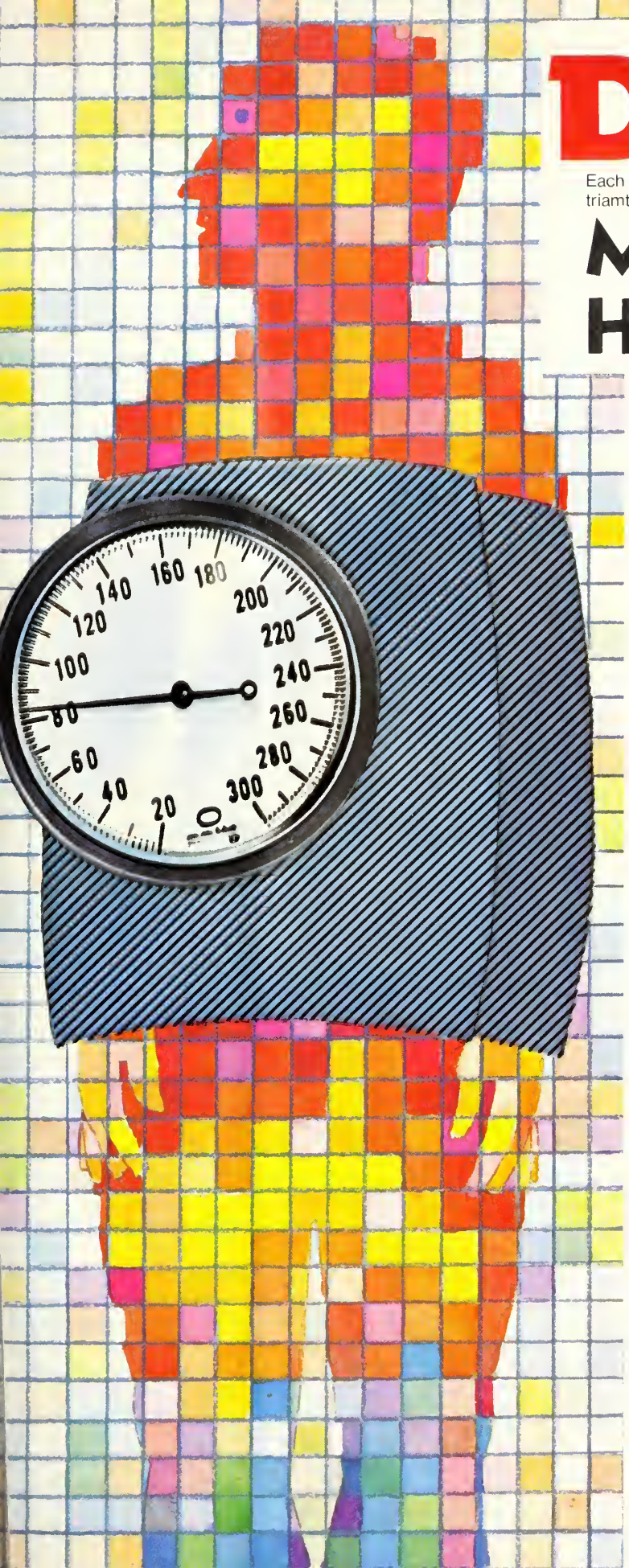

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INFORMATION

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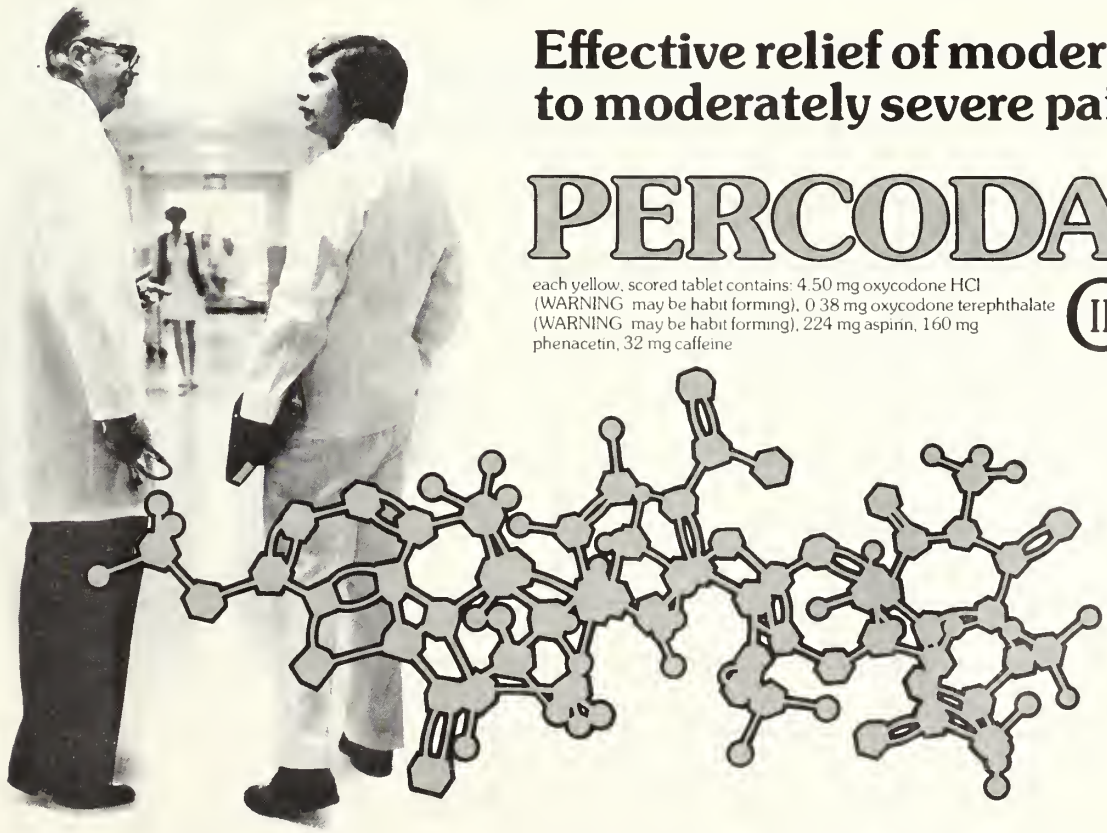

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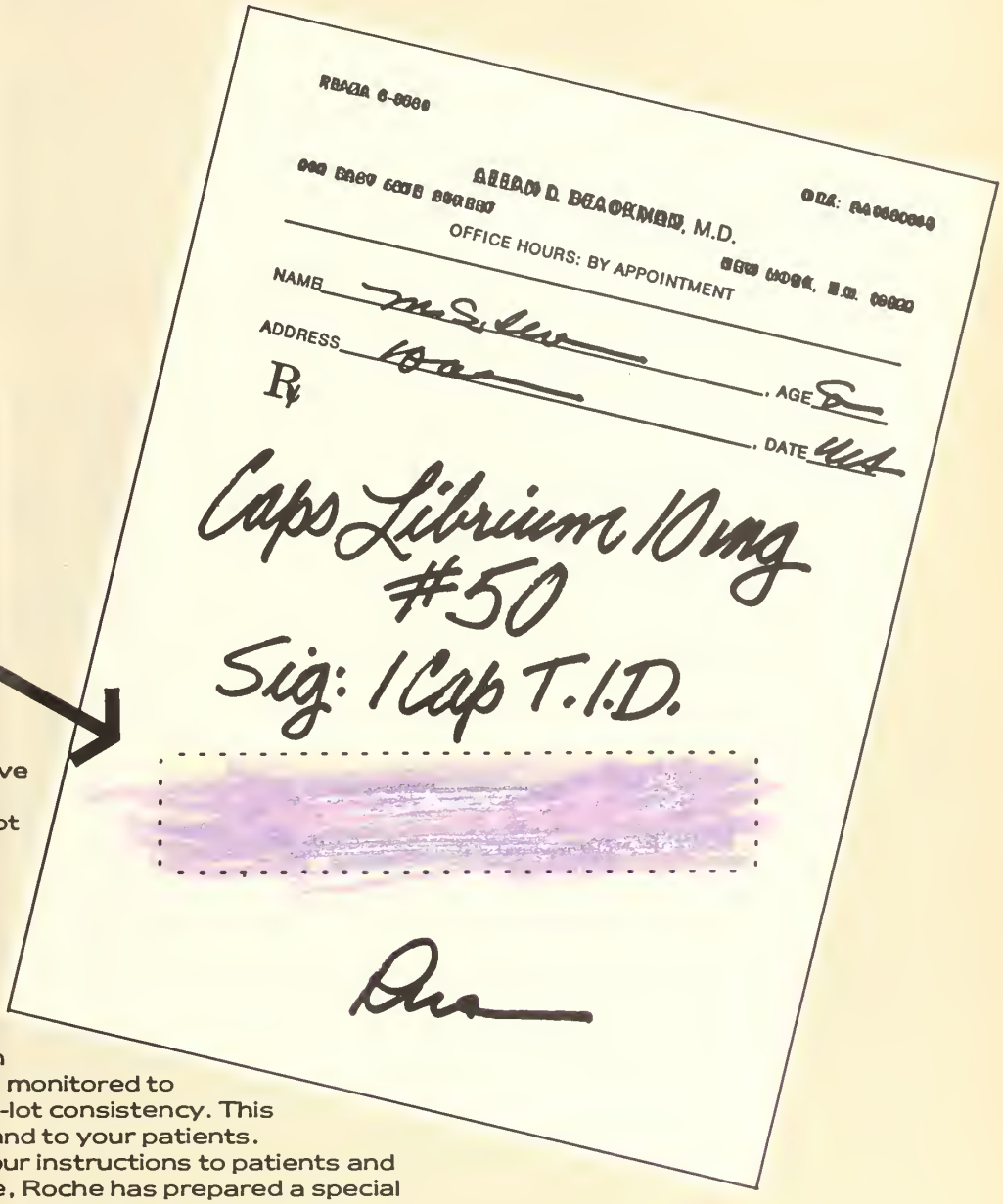

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Refer to: Fiala M, Chatterjee S, Ellis R, et al: Fever of undetermined origin—Role of cytomegalovirus and Epstein-Barr virus. West J Med 129:263-266, Oct 1978

Fever of Undetermined Origin

Role of Cytomegalovirus and Epstein-Barr Virus

MILAN FIALA, MD, *Los Angeles;* SATYA CHATTERJEE, MD, *Sacramento;*
RICHARD ELLIS, MD, *San Pedro, California;* BRUNO IMPARATO, MD, *Whittier, California;*
SAMI BAHNA, MD, *Torrance, California, and* ANDREW SAXON, MD, *Los Angeles*

Roles of various infections, neoplasms and granulomatous diseases in fever of unknown origin were studied in 22 patients. Bacterial infections were responsible in seven (32 percent), herpes viruses in five (23 percent), neoplasms in four (18 percent) and granulomata in two (9 percent) cases. Patients with herpes infections had initially no clinical or routine laboratory clues to viral involvement, and were given an intensive workup for 5 to 15 days. The diagnosis was made on the basis of cytomegalovirus or Epstein-Barr virus IgM antibody titers.

THE BASIC CATEGORIES of the syndrome of fever of undetermined origin (FUO) were established by Petersdorf and Beeson in 1961[1] based on an analysis of 100 cases, and were reviewed by Jacoby and Swartz[2] on the basis of 128 cases seen in the Massachusetts General Hospital between 1957 and 1971. These categories are infection (responsible for approximately 40 percent of cases), neoplasms (20 percent), collagen-vascular disease (15 percent) and miscellaneous conditions (25 percent). The definition of FUO most appropriate to the present-day medical practice is probably that of Wolff and co-workers[3]—that is, a syndrome comprising fever lasting at least 14 to 21 days in a patient who has received the usual office examination without a diagnosis being made. Some patients with FUO may be seen by a consultant, however, even before they experience fever for two weeks. The total duration of FUO may only be a few weeks, or it may be more prolonged, months or even years. Granulomatous hepatitis, temporal arteritis and other vasculitis, and juvenile rheumatoid arthritis are prominent causes of FUO with a duration over a year.[3-6] Most physicians spend little diagnostic effort on acute febrile illnesses of less than one week duration with respiratory or gastrointestinal symptoms suggestive of a viral cause. Considerable anxiety is engendered, however, if the illness lasts several weeks with spiking fever but is unaccompanied by the usual clues to infectious mononucleosis (young age, pharyngitis, lymphocytosis and abnormal liver function) or by manifestations of other well known viral diseases.

Patients and Methods

We have studied prospectively the cases of a group of 22 consecutive patients, presenting with a diagnosis of FUO in 16 hospitals in Los Angeles and Orange Counties between November 1976 and April 1977, for which an infectious disease

From the Departments of Medicine and Surgery, Martin Luther King, Jr., General Hospital, Charles R. Drew Postgraduate Medical School (Drs. Fiala and Chatterjee); University of California, Irvine (Dr. Fiala); Departments of Pediatrics, Microbiology and Immunology, UCLA School of Medicine (Dr. Saxon); Department of Pediatrics, Harbor General Hospital, Torrance (Dr. Bahna); San Pedro-Peninsula Hospital, San Pedro (Dr. Ellis), and Presbyterian Intercommunity Hospital, Whittier (Dr. Imparato). Dr. Chatterjee is now with the University of California, Davis, School of Medicine.

Submitted December 2, 1977.

Reprint requests to: Satya N. Chatterjee, MD, Department of Urology, UCD-Sacramento Medical Center, 4301 X Street, Suite 249, Sacramento, CA 95817.

ABBREVIATIONS USED IN TEXT

CMV = cytomegalovirus
EA = early antigen
EBNA = Epstein-Barr neutralizing antibody
EBV = Epstein-Barr virus
FUO = fever of undetermined origin

consultation was obtained. The patients had a usual office and admission examination before being seen by the consultant. Nine patients were male and 14 were female, with ages ranging from 13 to 79 years (mean of 46.5 years). The duration of fever at the time of the initial consultation varied between 5 and 120 days (median of 21 days).

Results

Infection was the largest category, comprising 14 (63.6 percent) patients (Table 1). Herpes viruses were established as the cause of infection in five patients (22.7 percent), in four cases the agent being cytomegalovirus (CMV), and in one case Epstein-Barr virus (EBV).

Reports of Cases

CASE 1. In a 36-year-old woman remittent fever (up to 105°F), cough and anorexia developed; she was admitted to hospital after a two-week febrile course. Hepatomegaly and pyuria were found on admission. In the peripheral blood smear, 43 percent leukocytes were lymphocytes and 14 percent were atypical lymphocytes. The proportion of lymphocytes increased to 59 percent one week after the admission. The patient was in hospital for 11 days until defervescence. CMV IgM titer was 32 whereas heterophil antibody was absent.

CASE 2. A 27-year-old woman was admitted to hospital following a two-week course with fever and one week with a petechial rash on lower extremities and the soft palate. She also had headache, myalgia and itching. In peripheral blood, 62 percent cells were lymphocytes with 14 percent atypical lymphocytes. The patient was discharged in five days. CMV IgM titer was 32 and IgG titer was 512.

CASE 3. In a 64-year-old man, father of the patient in case 2, fever, dependent petechial rash with a large ecchymosis in the left flank and atelectasis of the right lower lobe developed 23 days after the onset of the illness of his daughter. There were 64 percent lymphocytes in the peripheral blood smear, of which 17 percent were atypical. He was in hospital for eight days. CMV IgM titer was 128 and IgG titer was 1,024.

CASE 4. An 18-year-old-woman was admitted because of suspected meningitis with headache, stiff neck, fever and rash. Initial blood smear showed only 29 percent of lymphocytes but this

TABLE 1.—*Causes Established in 22 Patients Presenting With the Syndrome of Fever of Unknown Origin*

		Percent
Infection	(14)	63.6
Bacterial and fungal		
Bacterial endocarditis (1 due to Actinobacillus, 1 culture negative)	2	
Coccidioidomycosis	1	
Atypical mycobacteriosis (M gordonae)	1	
Pulmonary infection and heart failure	1	
Deep seated abscesses (2 abdominal, 1 chest)	3	
Viral		
Cytomegalovirus	4	
Epstein-Barr virus	1	
Undiagnosed	1	
Neoplasms	(4)	18.2
Myelomonocytic leukemia (and pulmonary tuberculosis)	1	
Lung tumor (unspecified)	1	
Liver adenoma (secondary to birth-control pills)	1	
Hepatoma	1	
Collagen vascular disease	(0)	
Miscellaneous causes	(4)	18.2
Granulomatous diseases		
Sarcoidosis	1	
Idiopathic granulomatous disease	1	
Factitious fever	1	
Recurrent pulmonary emboli	1	

proportion increased to 53 percent (with a few atypical lymphocytes) one week after admission. The patient was in hospital for five days. CMV IgM titer was 128 on the 9th day and 32 on the 53rd day of illness.

CASE 5. A 54-year-old woman had fever, headache and pronounced cervical adenopathy, as well as chronic otitis media. A total of 41 percent of leukocytes were lymphocytes on the 10th day and 52 percent on the 14th day. Heterophil titer was greater than one million; it was not reduced significantly by absorption with guinea-pig kidney, whereas beef red cells diminished the titer to 1,792. EBV IgM titer was 160, and EBV (virus capsid) IgG titer was also 160, whereas EBV early antigen (EA) titer was 200 and Epstein-Barr neutralizing antibody (EBNA) increased from less than 2 to 2. Fever resolved in 16 days but there was profound debility in convalescence. Chronic otitis media was unrelated to the patient's viral illness.

The diagnosis in all these five cases was established on the basis of EBV-specific IgM and IgG[7] or CMV-specific IgM[8] antibody titers determined by immunofluorescence, and CMV IgG titers assayed by complement-fixation. The average duration of hospital stays in these cases was 10 days (range 5 to 15 days). The diagnosis of an EBV-associated or CMV-associated illness was not apparent initially in any of the five cases. The patient in case 1 was thought to have a connective tissue disease, the patients in cases 2 and 3 either leptospirosis or rickettsial disease because of a febrile illness with petechial rash in two relatives, the patient in case 4 meningitis and the patient in 5 scrofula. The onsets of the illness in cases 2 and 3 (a woman and her father) were separated by one month, but the clinical presentation, with fever and rash, was identical.

In 8 cases (36.4 percent), bacterial and fungal infections were diagnosed by cultures or microscopic examination of blood, sputum, lung biopsy specimen or pus. Neoplasms were identified by histological examination of bone marrow or of surgical specimens in four patients (18.2 percent). Four patients (18.2 percent) had miscellaneous causes of FUO. Factitious fever was suspected in a female patient with a temperature of 40°C (104° F) but a normal pulse who had a prolonged history of psychoneurosis. One patient had a ventilation-perfusion lung scan characteristic of pulmonary emboli. The diagnosis of a granulomatous process was made with great difficulty in two patients. One was initially considered to suffer from histoplasmosis because of a generalized involvement of the reticuloendothelial system (hepatomegaly and splenomegaly and adenopathy) and an ulcer on the soft palate. The diagnosis of sarcoidosis was made when fungal cultures were negative, caseation was absent and granulomata with giant cells containing crystalloid inclusions were found in the lymph node. The second patient had noncaseating granulomata in the liver, lymph node, and bone-marrow biopsy specimens, and negative cultures for bacteria and fungi. Although the granulomata in the liver and a favorable response to steroids

TABLE 2.—*Clinical and Laboratory Data on Five Cases of FUO Caused by CMV or EBV*

Patient No.	Sex	Age (Years)	Duration of Fever (Days)	Highest Fever (°F)	Pertinent Clinical Findings	Post-onset (Days)	Lymphocytes (Atypicals) Per 100 Leukocytes	Viral Antibody Titers CMV IgM	CMV IgG	EBV VCA IgM	EBV VCA IgG	EBV EA	EBV EBNA
1	♀	36	25	105	Pyuria, hepatomegaly	14	43 (0)	...	512				
						22	59 (29)	32	...				
2	♀	27	19	102	Dependent petechial rash, soft palate	14	62 (5)	128	128				
					petechiae, headache, myalgia, pruritus	39	66 (27)	32	512				
3	♂	64	14	102	Dependent petechial rash,	8	44 (few)	...	512				
					Left flank ecchymosis,	17	64 (20)	128	1,024				
					atelectasis (RLL)	31	..	512	1,024				
4	♀	18	14	102	Headache, stiff neck, rash	3	29 (0)	...	...				
						8	53 (few)	128	64				
						53	..	32	64				
5	♀	54	16	103	Heterophil-positive, cervical adenopathy,	10	41 (0)	...	...	...	...	....	..
					headache; chronic otitis media	14	65 (39)	160	160	160	160	20 D	<2
					(unrelated finding)	41	52 (17)	320	320	320	320	40 D	2

EA = Early antigen
EBNA = Epstein-Barr neutralizing antibody
EBV = Epstein-Barr virus
CMV = Cytomegalovirus
RLL = Right lower lobe
VCA = Virus capsid antibody

were suggestive of idiopathic granulomatous hepatitis,[4] the presence of granulomata in the bone marrow was not characteristic of the latter disease. Negative findings on an x-ray study of the chest, negative angiotensin converting enzyme assay, and the histological appearance of granulomata argued against sarcoidosis.

Discussion

In the studies in the 1960's, the clinical role of EBV and CMV was described with emphasis on young adults with mononucleosis.[9-12] Both CMV and EBV have also been shown to cause a wide spectrum of illness[13-15] including fever lasting 30 days or longer,[9,16] involving subjects of widely different ages (newborn to 66 years for CMV,[13] 2 to 78 years for EBV[10,16]) and delaying the characteristic lymphocytosis after the first few weeks of illness.[16] These characteristics allowed us to anticipate that both viruses may be important causes of FUO in noninstitutionalized adults without initial presentation suggestive of mononucleosis. In our study, four of five patients with CMV or EBV illness had less than 50 percent lymphocytes per 100 leukocytes on initial smears, but a significant atypical lymphocytosis developed in all patients 10 to 15 days after onset of the illness. CMV may have a greater propensity for spread than has been expected in well-to-do middle-class adults as shown by the occurrence of CMV infection in a 27-year-old woman (case 2) and one month later in her 64-year-old father (case 3). These two patients resided in different households and met only once a week for dinner.

Peripheral blood lymphocytes were characterized by their surface markers in two patients. In a patient with CMV infection (case 4), 16 days after onset 74 percent lymphocytes were T cells and 23 percent were Fc receptor cells. The patient with EBV infection had, 14 days after onset, characteristic predominance of T lymphocytes (86 percent T-lymphocytes and 4 percent Ig-positive B cells).[17] On peripheral blood smear, most of the lymphocytes in this patient were type III Downey forms with plasmacytoid features. *In vitro* immunoglobulin or heterophil antigen synthesis by lymphocytes was evaluated by acrylamide gel electrophoresis of immune precipitates. Despite a very high heterophil agglutinin serum titer (the titers without absorption or after absorption with guinea-pig kidney were greater than 1,000,000; after absorption with beef erythrocytes, the titer was 1,792), her lymphocytes did not spontaneously produce immunoglobulins *in vitro* over 24 hours, except a trace of IgM, and no heterophil activity was found in the supernatant of cultured lymphocytes. When her lymphocytes were cultured in RPMI 1,640 medium containing radiolabeled amino acids, no new antigens were synthesized which would be precipitated by patient's serum antibodies and be detected on acrylamide gels.

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Rheumatoid Hand Deformities: Pathophysiology and Treatment

DAVID B. APFELBERG, MD; MORTON R. MASER, MD; HARVEY LASH, MD; RONALD L. KAYE, MD; MELVIN C. BRITTON, MD, *and* ARTHUR BOBROVE, MD, *Palo Alto, California*

Rheumatoid disease, as it affects the hand, is a disease of the synovium lining the joints and sheaths of the tendon. The proliferating synovium destroys the articular surfaces of the joint, interferes with the gliding mechanism of the tendons and weakens the supporting ligaments of the joints. The degree and variety of deformities is multifold.

Treatment of the rheumatoid hand is aimed at conservation and restoration of hand function, as well as prevention of future deformities. Rheumatologists, physical therapists and hand surgeons carry out important functions in the well-planned, integrated regimen. Surgical treatment of the rheumatoid hand deformity may alleviate pain, lessen deformity and improve function in selected cases. It should be integrated in the general medical management of a patient.

Treatment of tendon ruptures includes tenorrhaphy, tendon grafting and arthrodesis in the case of mallet finger deformity. The wrist joint is improved by synovectomy and carpal tunnel release is accomplished by median nerve decompression. Metacarpal phalangeal joint deformities may be treated by synovectomy or silastic joint replacement when there is destruction of the articular joint surface, severe subluxation, or persistent painful motion.

An estimated 3.6 million adults in the United States have rheumatoid arthritis according to a recent United States Public Health Service survey.[1] In about 75 percent of patients with rheumatoid arthritis involvement of the tendons and joints of the hand develops. Initial changes include synovial proliferation and swelling which may progress to joint destruction with severe loss of function. A fuller understanding of the pathological process of rheumatoid hand disease by primary physicians and improved surgical techniques by hand surgeons afford the opportunity for a team effort to alleviate pain, prevent or lessen deformity, and increase function in these crippled hands. This paper will discuss in detail rheumatoid involvement of the hand and wrist and the resultant deformities and loss of function. The indications for and techniques of surgical correction are correlated with the pathologic abnormalities.

From the Departments of Plastic, Reconstructive and Hand Surgery (Drs. Apfelberg, Maser and Lash); Rheumatology (Drs. Kaye, Britton and Bobrove), and Occupational Therapy Hand Rehabilitation Clinic, Palo Alto Medical Clinic.

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Reprint requests to: David B. Apfelberg, MD, Palo Alto Medical Clinic, 300 Homer Avenue, Palo Alto, CA 94301.

Pathophysiology

Rheumatoid arthritis is a disease primarily affecting the synovial membrane which lines the joints and tendon sheaths. Joint and tendon changes are secondary to the rheumatoid synovitis.

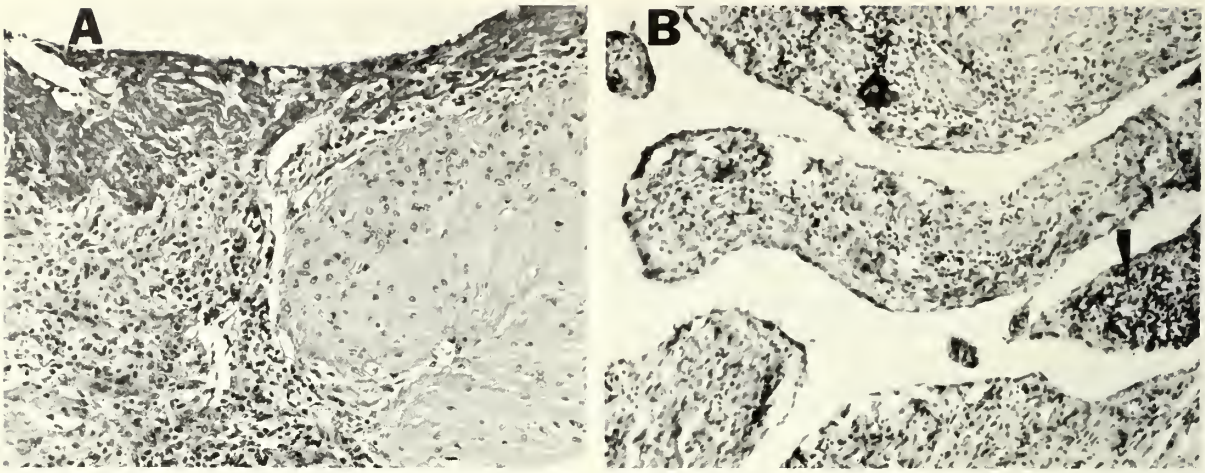

Figure 1.—Typical microscopic picture of rheumatoid arthritis illustrating **(A)** subsynovial fibrin of varying age with scant lymphocytic infiltrate and infiltrating granulation tissue (left pannus) exending over the articular cartilage, **(B)** Elongated and hyperplastic synovial villi with papillary hyperplasia and lymphocytic infiltrate and giant cell (arrow). (Photo courtesy Dr. John Maddox, Department of Pathology, Stanford University Medical Center.)

The normally thin synovial membrane proliferates to form a thick, villous edematous pannus. Microscopically, the synovitis is characterized by lymphocyte and plasma cell infiltration and increased vascularity with round cell infiltration, edema, and an increase in fibrous tissue in the perisynovial tissues (Figure 1).[2] The joint spaces become distended by overproduction of synovial fluid and proliferative synovium. The synovial reaction destroys the articular cartilage and attenuates the inflamed articular capsules and ligaments permitting the joints to be drawn into abnormal positions by muscle imbalance.[3] The diseased synovium surrounding the tendon invades the tendons with subsequent gradual dissolution of their normal fibers. There follows gradual stretching of the tendon, diminution in its strength and ultimately rupture. Dissolution of tendon may also be caused by interference with its blood supply by extrinsic pressure from the surrounding edematous tissues or bony prominences. The tenosynovitis disrupts the gliding mechanism of the tendon within the synovial sheath and limits tendon excursion.

Abnormalities at the Wrist

Early changes in the wrist include pain, swelling and limitation of motion. A proliferative synovial reaction may be visible on both the dorsal and palmar aspects of the wrist as a palpable, irregular, multilobular, boggy swelling. As the disease progresses, the restraining ligaments of the ulna gradually stretch and there follows a dorsal prominence of the ulnar styloid.[4] Several deformities are characteristic of advanced rheumatoid disease at the wrist. A flexion deformity of the wrist may result from the destruction of the radiocarpal joint and the relatively stronger action of the flexor muscles than the extensors of the wrist.[5] Grasping power of the fingers is reduced because of the check-rein effect of the stretched out long extensors of the fingers and the relatively slackened flexor tendons secondary to the flexed attitude of the wrist. The optimal function position of the wrist, about 30 degrees dorsiflexion, is lost.

Median Nerve Compression

The carpal tunnel syndrome of pain and paresthesia in the thumb, index, long and ring fingers, plus thenar atrophy, may be produced by rheumatoid involvement of the flexor retinaculum with median nerve compression. Similarly, proliferative synovium around the flexor tendons in the carpal tunnel may put pressure on the median nerve.[6] Other signs and symptoms include characteristic night pain, a positive Tinel sign (paresthesia produced by pressure or tapping over the median nerve area) and a reproduction of the symptoms by acute flexion of the wrist (Phalan test).[7] The diagnosis should be confirmed by neurophysiologic tests, such as electromyograms, nerve conduction velocities, and motor and sensory latency times across the wrist. The carpal tunnel syndrome may be one of the earliest manifestations of rheumatoid arthritis, hypothyroidism, gout, acromegaly or systemic lupus erythema-

tosus, and consequently the patient with this condition should be examined for these conditions and others.

Involvement of the Metacarpal Phalangeal Joints

Early manifestations of rheumatoid disease at the metacarpal phalangeal joints include pain, swelling, tenderness and limitation of motion. The joints become swollen periodically. In the later stages of the disease a flexion deformity of the metacarpal phalangeal joints with associated ulnar deviation of the finger is a constant finding in advanced rheumatoid disease. The lumbrical and interossei muscles are primarily responsible for flexion of the metacarpal phalangeal joints. Secondarily, these muscles act to extend the proximal and distal interphalangeal joints through their insertion into the extensor hood. Rheumatoid involvement of the intrinsic muscles produces spasm and subsequently fibrosis, thereby exaggerating the normal action of these muscles. The weakened metacarpal phalangeal joint is gradually drawn into acute flexion. Later, subluxation of the joint occurs. The ulnar deviation of the fingers is the end result of several factors: the relatively greater ulnar mobility of the metacarpal phalangeal joint, the pull of the lumbrical muscles, the obliquity in an ulnar direction of the metacarpal heads and the bow-string effect of the tendons which slip into the ulnar gutter adjacent to the joint.[8]

Involvement of the Fingers

Many varied abnormalities of the finger joints may be found in rheumatoid arthritis (Figure 2).[9,10] In fact, adjacent fingers in the same hand may exhibit a variety of altered pathological attitudes. The proximal interphalangeal joint may be hyperextended because of the intrinsic muscle contracture and the distal interphalangeal joint is flexed by the pull of the flexor profundus tendon which is tightened to its maximum by the hyperextended mid-joint. The profundus tendon thus flexes the distal phalanx in a check-rein fashion. This attitude of finger flexion of the metacarpal phalangeal and distal interphalangeal joints and hyperextension of the proximal interphalangeal joint is termed swan-neck deformity.

Mallet (baseball finger) deformity results from a rheumatoid tendon deformity which features attenuation of the insertion of the extensor tendon into the distal phalanx and a resultant incomplete extension of the distal phalanx. The Boutonniere deformity is caused by attenuation and rupture of the central slip of the extensor tendon at the proximal interphalangeal joint with resultant incomplete extension at this joint and hyperextension at the distal interphalangeal joint. Trigger finger or stenosing tenosynovitis is produced by the encroachment of the proliferating synovium in the flexor tendon sheath. The tendon is eventually notched and sticks in flexion.

Figure 2.—Typical finger and thumb deformities in rheumatoid arthritis. Metacarpal phalangeal joints illustrate ulnar drift and subluxation, ring finger of right hand shows swan-neck deformity, index and ring finger of left hand illustrate boutonniere deformity, midfinger of left hand has mallet finger deformity, and both thumbs have typical deformity.

The thumb undergoes changes not unlike those seen in the other digits. The metacarpal phalangeal joint is drawn into flexion and the interphalangeal joint into hyperextension. Opposition of the thumb is further impaired by degeneration of its carpal metacarpal joint.

Tendon Ruptures

Tendon ruptures occasionally precede other manifestations of rheumatoid involvement of the hand. The most commonly affected tendons, sites of rupture and resultant deformities are the extensor pollicis longus at the Lister tubercle at the distal radius producing incomplete thumb extension; tendons of the extensor digitorum communis to the ring and little fingers at the wrist joint producing finger drop, and the extensor carpi ulnaris tendon at the same area producing inability to dorsiulnar flex the wrist.[11]

Treatment

Since rheumatoid arthritis is a systemic disease, the major effort in treatment is directed at control of the entire disease process. The current medical treatment consists of rest, large doses of aspirin

and general supportive measures such as heat, paraffin baths, gentle physical therapy and protective night splinting. Local and systemic steroids, gold salts, and a wide range of anti-inflammatory agents have application under the direction of a rheumatologic specialist. Only when medical management fails to arrest the progression of the disease in the hands is surgical therapy indicated (Table 1). All authors agree that surgical operation is more effective if undertaken before extensive damage to the joints and tendons has occurred. Prevention of deformity by early operation will give far better results than multiple surgical procedures on the almost hopelessly crippled hand resulting from long-standing disease and progressive deformity resulting from many years of neglect. Surgical operation is now frequently done even during active stages of the disease, and is directed toward preservation and restitution of hand function, as well as prevention of future problems. Operation in many cases should be preceded by medical treatment and physical therapy in order to gain the greatest range of motion of stiff joints before operation.[12] Each hand is treated separately.

Wrist Joint

If a pronounced flexion deformity of the wrist joint is present, the grasping and pinching power of the hand will be severely impaired. In some patients, the carpal bones will have almost completely disintegrated and the wrist joint dislocated. Arthrodesis of this joint may be necessary,[13] but frequently a synovectomy will suffice in the early stages of the disease.[4] Transposition of the extensor retinaculum from above to below the extensor tendons and resection of the ulnar head are adjunctive measures to prevent eventual tendon rupture.[5]

Median Nerve Compression

When signs of median nerve compression within the carpal tunnel are observed, the nerve must be decompressed. In the early stages of this syndrome, temporary relief may be achieved by the instillation of steroids beneath the ligament and night splinting. Definitive treatment consists of excision of a portion of the transverse carpal ligament through its entire length. Removal of the hypertrophic synovium from the carpal tunnel will further decompress the nerve and protects the tendons from further damage.

Finger Joints

Stenosing tenosynovitis or trigger finger is corrected by excision of the thickened tendon sheath with resultant freeing of the tendon. Baseball or mallet finger, the result of disruption of the lateral extensor bands as they insert at the distal phalanx, is best treated by primary arthrodesis, although tendon grafts or transfers to the distal extensor tendons may occasionally be attempted. This joint is arthrodesed in approximately 15 to 30 degrees of flexion.

Boutonniere deformity is extremely difficult to correct. In some instances a free tendon graft is used to span the midjoint. Worthwhile improvement can also be obtained by a tenotomy of the extensor tendon over the joint which relieves the strong pull of the lateral extensor bands and allows the distal joints to come into flexion.[9] Swan-neck deformity may be treated by intrinsic muscle release and transfer of tendon tension along the finger extensor.[10]

Tendons

A tenosynovial reaction surrounding the flexor and extensor tendons frequently forms a large spongy cystic mass (Figure 3). Early removal of

TABLE 1.—*Summary of Rheumatoid Hand Deformities*

Area Involved	*Deformity*	*Correction*
Synovium	Synovitis	Synovectomy
Wrist	Dorsal, volar synovitis	Synovectomy
	Dorsal subluxation ulna	Resection ulnar styloid
	Flexion deformity	Arthrodesis, arthroplasty
Median nerve	Carpal tunnel compression	Release carpal tunnel, synovectomy
Metacarpal phalangeal joints	Synovitis	Synovectomy
	Ulnar drift, subluxation	Silastic arthroplasty
Fingers	Swan neck	Tendon transfer
	Mallet finger	Arthrodesis
	Trigger finger	Decompression tendon sheath
	Boutonniere	Tendon repair

the diseased synovium is a requisite for the prevention of continued destruction of the gliding surface of the tendons. The involved synovium is carefully dissected from the tendons.[11] Frequently the tendons will be found to be attenuated and in some cases completely disrupted. These tendons are repaired, if at all possible, by end-to-end anastomosis. When the tendon is destroyed over a great length, or when tendon integrity is tenuous, it is simpler to restore action with the appropriate tendon transfer of a tendon having a similar and synergistic action.[14] (Example: the extensor indicis proprius tendon is transferred into the distal extensor pollicis longus tendon for thumb extensor rupture.)

Figure 3.—Proliferative hypertrophic synovium surrounding and infiltrating extensor tendons at metacarpal phalangeal joints.

Metacarpal Phalangeal and Interphalangeal Joint

Synovectomy of the metacarpal phalangeal joints should be done early in the course of the disease to prevent destruction of the articular surfaces. At the time of synovectomy of the proximal joints, the extensor hood is repositioned to the radial side of the joint to correct the ulnar migration of these tendons.

Replacement of diseased joints by artificial ones has shown good results in many cases (Figures 4, 5). Swanson silastic prosthesic devices are the most commonly used, having been introduced in 1965.[15] The indications for the use of silastic prosthetic devices in the metacarpal phalangeal and interphalangeal joints include destruction of the articular joint surfaces with ulnar drift, severe

Figure 4.—Preoperative x-ray film of metacarpal phalangeal joints illustrating severe ulnar drift, joint destruction and subluxation.

Figure 5.—Postoperative x-ray film of metacarpal phalangeal joints after silastic replacement arthroplasty. Note straight position of fingers with prosthetic joint in place and stems in bony medullary canals.

subluxation and persistent painful motion. Prosthetic joint replacement may be undertaken even in the face of active disease. There is no untoward tissue reaction to prosthetic material, nor has any case of rheumatoid deformity been activated by surgical operation. The greatest subjective relief is often a diminution of pain, as well as greater hand function through improved position and greater mobility.

When the proximal interphalangeal joints are severely deformed or subluxed, arthrodesis is the treatment of choice. This provides a stable pain-free joint. The loss of flexion is compensated by motion in the metacarpal phalangeal and distal joints. Arthrodesis is also indicated for instability of the distal joint of the thumb. These joints are fixed in 30 to 40 degrees of flexion for maximal functional use.

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Airway Impairment and Hypoxia

REGARDLESS of whether you have an anesthesiologist there or not . . . if you are looking at the airway becoming impaired—(and it really doesn't matter if you're talking about a patient in the trauma room or somebody with a tumor in his larynx or edema in the larynx that you're watching)—the thing that is going to kill that patient probably is hypoxia. The body has extremely small oxygen stores, and if you exclude whatever amount of oxygen is in the lungs, the total body oxygen store in the average adult is of the order of about a liter. The body is consuming about 200 cc a minute . . . That being so, while you are watching and thinking, the patient should have oxygen. And I would say, even in our own institution, that a very common error is to be called for some horrendous problem and the patient is not on oxygen. So the number one thing is that while you're thinking, give the patient oxygen.

—H. BARRIE FAIRLEY, MD, *San Francisco*

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Organophosphate Pesticide Poisoning

STUART A. PEOPLES, MD, *and* KEITH T. MADDY, DVM, *Sacramento, California*

A total of 118 workers from a 120-person grape picking crew became ill in early September 1976. Of these (108 men and 10 women), 85 received medical attention and three of the 85 were admitted to hospital. The symptoms were typical for organophosphate poisoning. Average plasma and red cell cholinesterase values for the affected workers were depressed more than 60 percent. Most were treated with atropine and some were also treated with 2-PAM (pralidoxime). The exposure to residues of the organophosphate pesticides dialifor (Torak®) and phosalone (Zolone®) occurred in one grower's vineyards near Madera, California.

It appeared that workers had been allowed into recently-treated areas before the expiration of the required 30-day safety interval for dialifor, and that excessive skin exposure to residues of this pesticide had resulted. The clinical management of these cases and the occupational surveillance of the workplace became quite complex.

The grower sustained significant losses of grapes during the period in which some of his vineyards were under quarantine and he had to pay substantial medical expenses as well as a fine for violating state regulations concerning the proper use of pesticides.

Organophosphate pesticides decay more slowly under hot, dry weather conditions than they do when rainfall is frequent. California has imposed a number of specific safety intervals to be observed after the application of these pesticides to certain crops. If, in violation of these regulations, workers are permitted to enter fields too soon, poisoning can occur.

On September 8, 1976, out of a crew of 120 adults (110 men and 10 women), 15 field workers became ill while hand-harvesting grapes near Madera, California, in vineyards managed by one grower. The following day, 100 additional workers became ill; and 3 more on September 10.

The symptoms exhibited by the affected workers were typical for organophosphate poisoning. They included weakness, one-sided head pressure, nausea, vomiting, tight chest and blurred vision. Eighty-five of the ill workers received medical attention, three of these were admitted to hospital.

The medical treatment included outpatient treatment of approximately 60 of the workers by two Madera physicians, emergency room treatment of 25 workers by physicians at Madera Community Hospital, and the admission to hospital of three of the 25 workers seen in the emergency room. Most of the patients were treated with atropine and some were also treated with 2-PAM. Clinical recovery was prompt in most cases, but asthenia and other symptoms were a problem in several workers for a number of weeks.

Blood cholinesterase tests were conducted on the workers at the time of treatment. Plasma and

From the Worker Health and Safety Unit, California Department of Food and Agriculture, Sacramento.

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Reprint requests to: Stuart A. Peoples, MD, California Department of Food and Agriculture, 1220 N Street, Sacramento, CA 95814.

red blood cell values averaged 60 percent below normal levels. Interviews of all 120 workers showed that 33 of the workers who became ill had not sought medical attention; these workers had exhibited only mild symptoms of weakness, dizziness and blurred vision. All exposed workers (in addition to those initially treated) were examined by a physician and received blood tests as soon as the grower was required to furnish medical supervision.

A Madera labor contractor had provided the crew whose members became ill. The 1976 grape harvest began approximately two weeks before the first evidence of illness which was suspected as being due to exposure to cholinesterase-inhibiting compounds. The source of the workers' exposure was determined to have been pesticide residues in the vineyards of one grower, who farmed approximately 2,300 acres of grapes at several locations southeast of Madera, California.

Investigation

On September 10, 1976, the California Department of Food and Agriculture (henceforth referred to as the Department) was notified of the illnesses, and personnel were assigned to investigate the incident. The Environmental Protection Agency, Region IX, the California Department of Health, and the California Division of Industrial Safety (CAL-OSHA) were immediately notified. Prior agreement has designated the Department as the primary enforcement agency in this type of occupational exposure incident.

Personnel from the Madera County Agricultural Commissioner's Office immediately obtained grape foliage and fruit samples from the vineyard locations where the workers had been harvesting when they became ill. Samples were also taken from vineyards that the workers had harvested immediately before the onset of their illnesses. These samples were sent to Department laboratories for analysis. The Department's two mobile Pesticide Residue Laboratories were moved to Madera to help analyze the large numbers of leaf and grape samples that were drawn. Laboratory findings of pesticide residues often did not correspond with the grower's pesticide application records.

The grower's records of pesticide applications were reviewed to determine the workers' probable exposure to pesticide residues before the onset of the illnesses, as well as their possible further exposure were the harvest allowed to continue.

The high levels of dialifor (Torak®) and phosalone (Zolone®) residues found on the foliage of vines in certain locations did not support the grower's records of application date, volume and rate per acre of application for the pesticides in question. Comparison of these high residue levels with samples collected in previous years for studies by the University of California and by the Department indicated either a later date of application, at least for dialifor, or a higher rate of application than had been indicated by the grower's records.

Regulatory Actions

On September 13 an order was issued by the Department to the grower, prohibiting any of the workers who became ill from returning to the unharvested section of the suspect field.

On September 15 orders were issued to the grower and his three labor contractors requiring that any employee hand-harvesting grapes in any of his vineyards be provided with medical supervision. This required medical supervision for all pickers was to include periodic plasma and red cell cholinesterase tests and periodic examination by a physician to look for signs or symptoms of organophosphate poisoning. A prohibition of the harvest of grapes at two specific locations was also included in this same order.

That same day, the grower obtained the services of a physician as medical supervisor. On September 16 a mobile medical laboratory was set up at the vineyard where harvest was continuing, and specimens of the workers' blood were drawn by a laboratory technician for cholinesterase determination. The workers were examined by the medical supervisor. Following these examinations and subsequent ones, the workers were issued an identification card and were instructed to carry it with them. All new workers who were brought in to hand-harvest grapes on the grower's other properties also had their blood drawn and analyzed for cholinesterase levels; all of their cholinesterase enzyme levels were in normal ranges. None of the new employees became ill or experienced cholinesterase level depression while harvesting.

Commencing September 17, 1976, personnel from the Department and the Madera County Agricultural Commissioner's Office began a daily inspection of the workers entering the vineyards. The workers' identification cards were checked to verify that they were under medical supervision

and the workers were observed to be sure that they were wearing clean outer clothing at the beginning of each work day. Workers who had no evidence of being under medical supervision or were not wearing clean outer clothing were not allowed to work.

The grower and medical supervisor made arrangements for a medical laboratory technician to be present on several occasions to draw blood specimens from workers arriving at the ranch for the first time for employment as grape harvesters. Several hundred persons who had been harvesting grapes in other locations in the San Joaquin Valley were screened in this way on arrival and none was found to have low cholinesterase levels.

The medical supervisor returned to the ranch a number of times to examine workers individually for signs of organophosphate poisoning. All depressed cholinesterase levels found in blood samples during these follow-up visits were found only in the first work crew of 120 persons who had been poisoned and there was no evidence of further depression in these same workers after the initial exposure. Those workers from the initial poisoning episode who were found to have severely depressed cholinesterase levels were ordered by the medical supervisor not to engage in any activity that would involve substantial body contact with treated foliage; these employees were assigned to other tasks on the ranch. Those workers with moderate cholinesterase depressions were allowed to continue work in those fields found to have no residues, or very low residues of organophosphate or carbamate pesticides on the foliage.

On September 22 the order prohibiting the harvest of grapes at one location was amended after laboratory tests showed a degradation of the residue levels on the fruit and foliage. This vineyard was released to be hand-harvested. No employee from the work crew originally poisoned was permitted to harvest in this vineyard. On October 1 the order issued prohibiting the harvest of a second block of grapes was amended to permit the hand-harvesting of a section of this field, with similar restrictions on persons who were allowed to pick. Pesticide residue levels on the fruit and foliage had been found to have decayed to a safe level.

Subsequent to the initial issuance of an order prohibiting the harvest in a third vineyard the grower had attempted to remove some of the residues from the fruit and foliage by washing this vineyard with a soap and water solution applied with a motorized pesticide spray rig. In addition to this washing, a rainstorm helped to reduce the amount of pesticide residues present, as verified by laboratory analysis. On October 5 this order was amended to permit the machine-harvest of these grapes remaining under quarantine. Hand-harvesting of this vineyard was not permitted due to high residue levels of dialifor still remaining on the foliage, even though residue levels on the fruit itself were below the legal tolerance of 1 ppm permitted for human consumption of grapes. The driver of a machine harvester rides far above the grape foliage.

Estimates were made of the levels of pesticide residues to which the original work crew had been exposed before the onset of the illnesses. These estimates were based upon comparison of pesticide residue level at the time of sampling, the dates of harvest, and the dates and rates of application with the results of available pesticide residue degradation studies.

Workers had been exposed to foliage containing up to 57 ppm of phosalone and up to 2.3 ppm phosalone oxon. Carefully conducted studies of workers in citrus groves and peach orchards during the summer seasons of 1974, 1976 and 1977 in this same locale did not show significant cholinesterase depression or illness when workers were exposed to levels of phosalone and phosalone oxon residues on foliage which were higher than these actually measured levels. Therefore, these levels of phosalone or phosalone oxon (or both) on grape foliage were not considered to present a toxic hazard to persons picking grapes by hand.

It appears that the workers had been exposed to residues of up to 100 ppm of dialifor and more than 2 ppm of dialifor oxon when working in the three different locales. These levels of dialifor and dialifor oxon were determined to have been toxic to the workers harvesting these grapes. The investigation led to the conclusion that a number of rows in several vineyards had apparently been treated late in the season, and that probably only about half of the required 30-day worker safety interval had passed when workers were exposed to the residues of dialifor and dialifor oxon.

Within two weeks after this poisoning incident occurred, foliage and grape samples were collected from 79 other vineyards that had been treated with dialifor. Blood specimens were collected from workers harvesting grapes in these

vineyards. Growers and workers were interviewed concerning work experience in these other vineyards. No evidence was found concerning adverse health effects associated with working in these other vineyards.

Discussion

Since 1949 California has had experience with poisoning of field workers exposed to residues of organophosphate pesticides. The state has imposed worker safety reentry intervals for organophosphates on a number of crops. In most cases when poisoning of this type occurs there usually is evidence that entry was not in compliance with specified intervals. The Federal Environmental Protection Agency at present is evaluating California's approach to protection of field workers. It appears that they may require adherence to safety intervals for more pesticides and crops than are required now and for longer periods than the current average length of 48 hours for the Federal Safety Intervals. Many of the required safety intervals in California exceed seven days.

Several recent studies by the Department on foliage residues at the time of harvest, and of blood and urine studies of field workers by the Department and the University of California at Davis, indicate that almost all growers are adhering to prescribed preharvest and worker safety intervals.

It is significant that several hundred new workers brought in from other vineyards in the San Joaquin Valley had normal cholinesterase levels upon arrival at the ranch where pesticide misuse had led to the above-mentioned poisoning incident. During the same month in which this poisoning incident occurred the University of California at Davis was in the midst of a study on grape pickers. The study was underway in a nearby county in which the rates of organophosphate pesticide application for grapes are the highest in the San Joaquin Valley. No depressed cholinesterase levels were noted among these workers.

As for the medical management of this specific incident, it was determined that most of the workers desired to return to work within a few days of the onset of illness and treatment. They wanted to avoid being assigned a lower-paying nonpicking job or being placed on disability compensation at a lower rate of pay. The medical supervisor had ordered that the vineyards with high levels of foliage residues would not be harvested by hand even though the grapes met tolerance requirements; these three vineyards were placed under quarantine. For the vineyards that had foliage with appreciable (but not high) levels of organophosphate residues (previously considered nontoxic for normal workers) the medical supervisor allowed harvest by workers with normal cholinesterase levels and by some workers with moderate but not severe depression of cholinesterase values. For the workers with severely depressed cholinesterase levels, the medical supervisor permitted work only at jobs that either did not involve contact with foliage or involved picking in fields with no organophosphate or carbamate residues present.

In the process of analyzing the cholinesterase level data for workers at the close of the picking season on this ranch, it was noted that of the originally exposed workers, although further depression of the low cholinesterase levels did not occur while under medical supervision, the return of levels toward normal was slower than considered desirable. In retrospect it appears that workers with significantly depressed cholinesterase levels, but who appear to be clinically normal, should be assigned only to jobs picking crops in fields where there are no detectable levels of organophosphate or carbamate pesticide residues or assigned to other jobs where no such exposure would be expected to occur. If such work could not be found they should be placed on disability compensation until their cholinesterase levels return to normal.

Poisoning of field workers by exposure to pesticide residues on foliage in a treated field is not a problem commonly diagnosed and reported by physicians. Most reported occupational exposures to pesticides in California occur in persons involved in mixing, loading and applying pesticides. It is possible that there is some underdiagnosis and underreporting of such incidents.

Of the 1,746 physicians' reports filed in 1975 that contained a suggestion of possible pesticide involvement in an occupational exposure, 240 were classified as involving employed persons who were exposed to pesticides with no obvious illness resulting (primarily firemen and policemen), another 163 were placed in a category of unconfirmed or negative for actual pesticide exposure. It appears that about 1,343 of the cases may have resulted from actual pesticide exposure. Of these, 797 were only eye or skin problems; although these can be very troublesome, they all appear to have been treatable without permanent adverse

effects. Only 546 persons developed systemic effects attributed to pesticide exposure. This group deserves very careful study and attention. Most of these persons were not ill for more than a few days and chronic problems apparently did not often occur.

In 1975, in the category of field workers exposed to pesticide residues, there were 28 systemic, 115 skin, 21 eye, and 3 eye and skin cases reported by physicians. Most of the systemic illnesses occurred as a result of one incident in which the grower allowed citrus harvesters to pick before the safety interval for ethyl parathion had expired. In this incident, the grower experienced crop losses due to the quarantine imposed, and paid sizable medical expenses and a fine for violation of state regulations.

Deaths attributable to occupational pesticide exposure rarely occur in California. Four such deaths have occurred since 1971. In 1972 an applicator in a peach grove became intoxicated from drinking alcoholic beverages while working, spilled some parathion upon himself, and died; a jail trustee working as a gardener drank paraquat from an unlabeled wine bottle and died. In 1973 a structural pest control worker died and in 1975 another structural pest control worker died—both when cyanide was grossly mishandled and illegally used indoors. In 1974 there were no occupational deaths. (In 1975 in California, there were 20 deaths attributed to pesticides: occupational, 1; accidental or homicide, 1; homicide, 1, and suicide, 17. This has been the typical pattern for pesticide-caused deaths in recent years in California.)

The large number of acutely ill patients in this incident severely taxed the medical resources of the physicans involved with the result that they directed their attention to giving emergency treatment which left no time for filling out required state forms. This was made increasingly difficult by the fact that few patients spoke English, and that they left after being treated and before the physicians could get the necessary information. The physicians believed that they had neither the time nor facilities for locating these workers; therefore, few reports were filed.

Concerns were expressed by several groups representing the workers' interests that the lack of complete reporting of each case on appropriate forms separately to the Division of Industrial Safety and to the Department of Health allowed for continued underreporting of this type of pesticide exposure and interfered with the worker's right to file a claim for workman's disability compensation.

Early in 1977 an inquiry about pesticide poisoning of workers in general and about this specific incident was conducted by a committee of the Senate of the California Legislature. Later in the legislative session, a new law (AB 1307) was enacted which went into effect in January 1978. This new law requires that all suspected pesticide illnesses be reported to the county health officer by telephone within 24 hours. In the case of occupatonal reports, one copy of the Doctor's First Report of Work Injury is to be mailed to the county health officer within seven days. Details of these reporting requirements can be obtained from the county health departments.

Appendix

Some useful sources of medical information for physicians about pesticides include the following:

Addresses	*Telephone Numbers*
California Department of Health, Pesticide Study Unit 2151 Berkeley Way Berkeley, California 94704	(415) 843-7900 Ext. 505
California Department of Food and Agriculture, Medical Consultant 1220 N Street Sacramento, California 95814	(916) 445-8400
Donald Morgan, MD (EPA Consultant) Iowa Epidemiologic Studies Program University of Iowa Medical School Iowa City, Iowa 52240	(319) 353-5558 or 338-8474
Sacramento Poison Center Sacramento Medical Center 2315 Stockton Blvd. Sacramento, California 95817	(916) 453-3692
San Diego Poison Control Center University Hospital 225 W. Dickson Street San Diego, California 92103	(714) 291-4000
Los Angeles (Thos. Fleming) Poison Center Children's Hospital of Los Angeles 4650 Sunset Blvd. Los Angeles, California 90054	(213) 664-2121
Denver Poison Center Denver General Hospital 301 W. 7th Street Denver, Colorado 80204	(303) 629-1123
Chevron Chemical Company Research Laboratories 940 Hensley Way Richmond, California 94806	(415) 233-3737
Dow Chemical Company 2030 Dow Center Road Midland, Michigan 48640	(517) 636-4400
Shell Chemical Company 2401 Crow Canyon Road San Ramon, California 94583	(415) 837-1531 or 837-3120

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The Pathophysiology and Clinical Aspects of Hypercalcemic Disorders

DAVID B. N. LEE, MD; EDWARD T. ZAWADA, MD, *and*
CHARLES R. KLEEMAN, MD, *Los Angeles*

For the purposes of this review, the vast and increasingly complex subject of hypercalcemic disorders can be broken down into the following categories: (1) Physiochemical state of calcium in circulation. (2) Pathophysiological basis of hypercalcemia. (3) Causes of hypercalcemia encountered in clinical practice: causes indicated by experience at the University of California, Los Angeles; neoplasia; hyperparathyroidism; nonparathyroid endocrinopathies; pharmacological agents; possible increased sensitivity to vitamin D; miscellaneous causes. (4) Clinical manifestations and diagnostic considerations of hypercalcemic disorders. (5) The management of hypercalcemic disorders: general measures; measures for lowering serum calcium concentration; measures for correcting primary causes—the management of asymptomatic hyperparathyroidism.

PHYSICOCHEMICAL STATE OF CALCIUM IN CIRCULATION

TOTAL SERUM CALCIUM (Ca) concentration represents the sum of three fractions: protein-bound calcium (CaProt), diffusible calcium complexes (CaR) and ionized calcium (Ca^{++}). Ca^{++} and CaR constitute the total ultrafiltrable calcium. Figure 1 graphically depicts the various components of calcium measured in 29 normal subjects.[1] For clinical purposes, 50 percent of total serum calcium concentration may be taken as an approximation of the Ca^{++} concentration. Although both the CaProt and CaR fractions may be important in some disorders of calcium homeostasis, the overwhelming majority of clinically important disturbances in serum calcium affect the Ca^{++} fraction. Physiologically this is the component that is critically regulated and maintained, and it is with this component that our present review is concerned. However, a few clinically important comments are in order regarding the CaProt and CaR fractions.

The major fraction of the CaProt consists of calcium bound to albumin[1,2] (estimates vary from 50 percent[2] to 90 percent[1]) with about 10 percent to 15 percent bound to globulins. In 1935 McLean and Hastings[3] proposed that the relationship

From the Medical and Research Services, Wadsworth Veterans Administration Hospital Center (Los Angeles) and Veterans Administration Hospital (Sepulveda), and the Division of Nephrology, Department of Medicine, UCLA School of Medicine, (University of California, Los Angeles).

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Reprint requests to: David B. N. Lee, MD, Division of Nephrology, Department of Medicine, UCLA Center for the Health Sciences, Los Angeles, CA 90024.

ABBREVIATIONS USED IN TEXT

3′,5′-AMP = 3′,5′-adenosine monophosphate
Ca = calcium
Ca^{++} = ionized calcium
cAMP = cyclic adenosine monophosphate
CaProt = protein-bound calcium
CaR = diffusible calcium complexes
ECF = extracellular fluid
EDTA = edetate (ethylenediaminotetraacetate)
GC = glucocorticoids
GFR = glomerular filtration rate
iPTH = immunoreactive parathyroid hormone
MEA = multiple adenomatosis syndromes (multiple endocrine adenomatosis)
MRC units = Medical Research Council units
OAF = osteoclast activating factor
PGE = prostaglandins of the E series
PHPT = primary hyperparathyroidism
PTH = parathyroid hormone
RECaP = rapidly exchangeable calcium pool
TRCa = tubular reabsorption of calcium
TRP = tubular reabsorption of phosphate
VIP = vasoactive intestinal peptide
ZE = Zollinger-Ellison (syndrome)

between Ca^{++} and the concentration of protein in the blood may be represented by the mass action equation:

$$\frac{(Ca^{++})\ (Prot^{-})}{(CaProt)} = K = 10^{-2.22 \pm SD\ 0.07}$$

(temperature 25°C, pH 7.35)

where $Prot^{-}$ is equal to the concentration of plasma protein, primarily albumin. Since K is a constant, the numerator and the denominator must change proportionately in any physiologic or pathologic state. Although such formulation may be an oversimplification, the predicted Ca^{++} from the nomogram of McLean and Hastings generally agrees well with observed values obtained by the original frog heart bioassay method for Ca^{++}[3] and by direct chemical and calcium electrode measurements.[1,4] The day-to-day fluctuation in total serum calcium concentration in normal subjects is almost totally accounted for by corresponding change in CaProt. The Ca^{++} is maintained within a very narrow range.[5,6]

The relationship between albumin and CaProt in normal human subjects and patients with various protein disorders is illustrated in Figure 2.[7] It is apparent that albumin binds calcium in a predictable manner under all conditions studied. Approximately 1 mole of albumin binds 1.23 moles of calcium, or 1 gram of albumin binds 0.713 mg of calcium. In practice, a change in serum albumin concentration of 1 gram per dl may be expected to result in a change of total serum calcium concentration of 0.8 mg per dl in the same direction. The calcium-binding property of different fractions of globulins differs in different clinical situations. α-globulins appear to have no calcium binding capacity; β-globulins bind calcium in normal subjects and in patients with non-myeloma forms of hypergammaglobulinemia; and γ-globulins, which do not bind calcium in normal subjects, are found to bind calcium in patients with multiple myeloma.[2] Although in patients with multiple myeloma in whom an increase in Ca concentration develops there is a

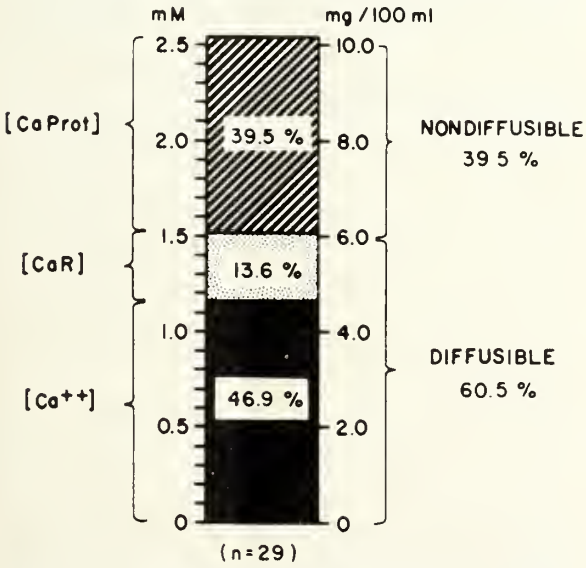

Figure 1.—Components of serum total calcium obtained from ultrafiltration data in 29 normal subjects. Indicated percentages are the mean values for the group. (Reprinted from Moore[1] with permission.)

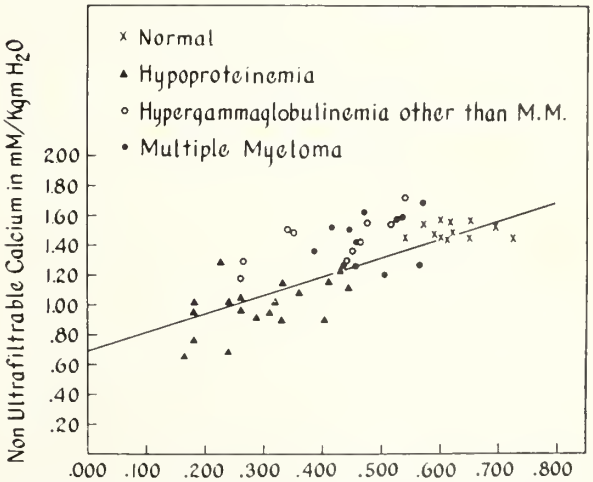

Figure 2.—Albumin-calcium relationship in normal subjects and patients with various protein disorders. (Reprinted with permission from Prasad and Flink.[7])

true increase in Ca^{++}, in rare instances the hypercalcemia may be totally accounted for by the increase in CaProt[8] which is physiologically nondisruptive.

Changes in CaProt may result from either a change in plasma protein concentration or a change in protein calcium-binding capacity. If a tourniquet is applied for three minutes before obtaining a blood sample, transudation of protein-free fluid out of the capillaries will result in concentration of the plasma proteins and a rise in the protein-bound calcium. This phenomenon may account for a mean increase of 22 percent for serum protein, 10 percent for serum calcium and 4 percent for serum magnesium.[9] A similar mechanism of *in vivo* ultrafiltration probably also accounts for the known influence of posture on Ca.[6] In this respect, blood collection in the sitting position is probably the most practical form of standardization.

Changes in serum sodium and hydrogen ion concentrations are known to be capable of altering the protein binding capacity for calcium. Walser showed that severe hyponatremia (less than 120 mEq per liter) and hypernatremia (greater than 155 mEq per liter) cause predictable changes in Ca concentration secondary to changes in calcium binding properties of plasma proteins.[10]

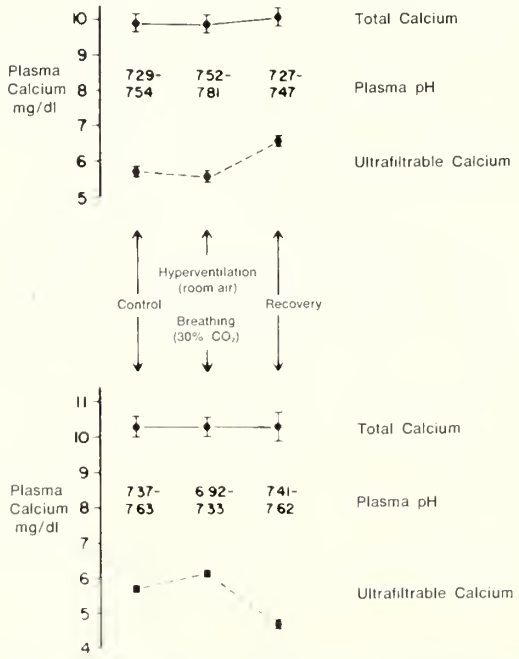

Figure 3.—Rebound increase in plasma ultrafiltrable calcium during recovery phase from respiratory alkalosis and acidosis [data derived from Prasad, Brown and Flink[11]].

Hyponatremia causes an increase in CaProt and, therefore, slight hypercalcemia, while hypernatremia causes a decrease in CaProt and, therefore, slight hypocalcemia. In neither case is the concentration of Ca^{++} altered. Consistent pH effects on Ca^{++} have been observed in both serum and whole blood. Ca^{++} varies inversely and CaProt varies directly with pH. Therefore, an increase in pH leads to a decrease in Ca^{++} and a corresponding increase in CaProt. The total calcium concentration may remain unchanged. Average change in serum Ca^{++} for 1.0 unit pH change is 0.42 mmole per liter (1.68 mg per dl) in the opposite direction.[1]

A rebound phenomenon in ultrafiltrable calcium concentration has been observed in dogs recovering from respiratory alkalosis and acidosis.[11] Ultrafiltrable calcium decreases slightly during respiratory alkalosis, but a clear rebound increase is seen during the recovery phase (Figure 3). A similar but reverse series of changes is seen in respiratory acidosis and during recovery. The posthypercapnic reduction in ultrafiltrable calcium may be an important contributory cause in the development of fatal ventricular fibrillation —a complication previously attributed solely to hyperkalemia.[12] A similar mechanism may be responsible for certain unexplained postsurgical deaths in man.[13] The fatalities usually occurred after rapid reduction of carbon dioxide tension which became elevated during anesthesia.

While the citrate ion is the most potent calcium-complexing agent in blood, calcium citrate accounts for only 3 percent of the bound calcium and therefore plays an insignificant role in the binding and transport of calcium in plasma or body fluids. The practice of routine administration of calcium salts during massive citrated blood replacement is now considered unwarranted and is probably dangerous.[14-16] During the treatment of hypercalcemia with edetate (ethylenediaminotetraacetate [EDTA]), Ca^{++} may be progressively complexed in the absence of commensurate changes in total calcium concentration. Ca^{++} concentration measurement is therefore more meaningful than that of total calcium levels in gauging the effect of EDTA therapy, especially before renal excretion of the complexed Ca is fully augmented. Calcium may also form complexes with heparin. Consequently, heparinized whole blood Ca^{++} concentration may be less than that in the corresponding serum.[1] Finally, hypercalcemia associated with experimental acute uremia induced by bilateral

nephrectomy has been attributed to a rise in serum citrate level and an increase in calcium-citrate complexes.[17]

With the development of specific electrodes which allow direct measurement of Ca^{++}, a number of reports have evaluated the usefulness of measuring Ca^{++} versus total serum Ca concentration in the diagnosis of hypercalcemic disorders.[1,4,18] In general, a close correspondence is observed between directly measured Ca^{++} values and those predicted from established nomograms.[1,4] In one study, Ca^{++} and total Ca concentrations were measured in 149 serum samples from 48 patients with hyperparathyroidism.[18] Although better diagnostic accuracy was achieved by Ca^{++} measurements, hypercalcemia was detected in all patients upon repeated testing using either method of measurement. Several groups of workers, however, have advocated clear diagnostic superiority of Ca^{++} determinations in a number of calcium homeostatic disorders.[19-22]

PATHOPHYSIOLOGICAL BASIS OF HYPERCALCEMIA

Hypercalcemia generated by a direct intravenous infusion of calcium at a rate of 9.8 mg per kg of body weight per hour is illustrated in Figure 4.[23] As soon as the infusion was stopped, recovery occurred promptly and normocalcemia was restored within three hours. Recovery from acutely induced hypocalcemia was equally rapid and complete. Garty and associates[24] also found a prompt correction of induced hypercalcemia (18 to 20 mg per dl) at a time when only 10 percent to 15 percent of the infused load was excreted. The "buffering" of such calcium loads has been attributed to the rapid exchange of the administered calcium with a metabolically active part of the skeleton which is in dynamic equilibrium with the extracellular calcium pool.[23,25] The efficiency of this rapidly exchangeable calcium pool (RECaP) in buffering acute changes of extracellular fluid (ECF) calcium concentration is in some way influenced by the prevailing metabolic state of the skeleton. For example, in chronic parathyroidectomized dogs, in which normal plasma calcium concentration is maintained by high oral calcium intake, the buffering capacity against acute changes in ECF calcium levels is notably impaired.[26] On the other hand, when normocalcemia in these animals is maintained by vitamin D (which increases bone turnover activities), the buffering capacity against induced hypocalcemia is improved to a pronounced degree, although not completely restored.[27] The rate of recovery from induced hypocalcemia is also enhanced in pathophysiological states characterized by increased skeletal turnover activities—for example, in normal growing dogs and in dogs given pharmacological doses of parathyroid hormones.[28] Recovery from induced hypocalcemia is also accelerated with growth hormone administration.[29] Pretreatment with imidazole, a stimulant of adenosine 3′,5′-phosphodiasterase activity, which increases degradation of cyclic 3′,5′-adenosine

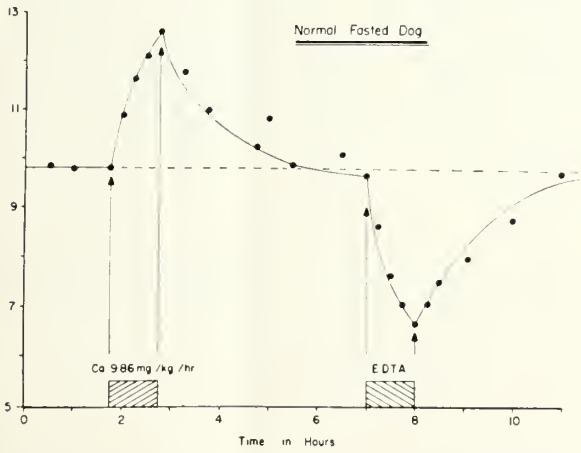

Figure 4.—Acute homeostasis of calcium in a fasted adult dog. Dose of calcium was 10 mg per kg of body weight as gluconate, given by continuous intravenous infusion over a one-hour period. Dose of edetate (EDTA [ethylenediaminotetraacetate]) was sufficient to chelate 10 mg of calcium per kg of body weight over the same period. (Reprinted from Copp[23] with permission.)

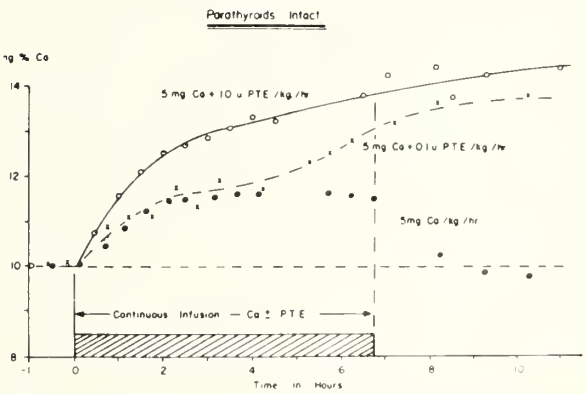

Figure 5.—Effect on plasma calcium level of continuous infusion of 5 mg of calcium per kg of body weight per hour for a period of seven hours: with no added parathyroid extract (PTE) (dotted line); with simultaneous infusion of 0.1 unit of PTE per kg of body weight per hour (broken line), and with simultaneous infusion of 1.0 unit of PTE per kg of body weight per hour (solid line). (Reprinted from Copp[23] with permission.)

monophosphate (3′,5′-AMP), reduces the response.[28] In man, the increased sensitivity of hypoparathyroid[30] and hypothyroid[31] patients to oral calcium loads may be the result of an impairment in buffering capacity of this RECAP secondary to a reduced rate of bone turnover and metabolic activity.

When calcium is infused at a constant rate of 5 mg per kg of body weight per hour for several hours in a dog with intact parathyroid glands, an equilibrium with sustained hypercalcemia of 11.6 mg per dl is established (Figure 5, dotted line).[23] The stabilization of the hypercalcemia suggests that the removal of calcium from ECF through bone uptake and urinary excretion has balanced the calcium added to ECF through infusion. Since the increase in calcium excretion was known and accounted for 0.5 mg per kg per hour, net movement of calcium into bone must account for the remaining 4.5 mg per kg per hour of calcium infused. This net bone-ward movement of calcium appears to depend on plasma calcium concentration. Figure 6 illustrates the plasma calcium levels in an 8-week-old parathyroidectomized pig in which the rate of calcium infusion was progressively increased.[23] It can be seen that with each increment in the rate of calcium infusion, a new equilibrium was attained at a higher plasma calcium concentration. This suggests that the addition of calcium into ECF would lead to a progressive elevation in calcium concentration which, in turn, would result in increasing net bone calcium sequestration until a new equilibrium is reached.

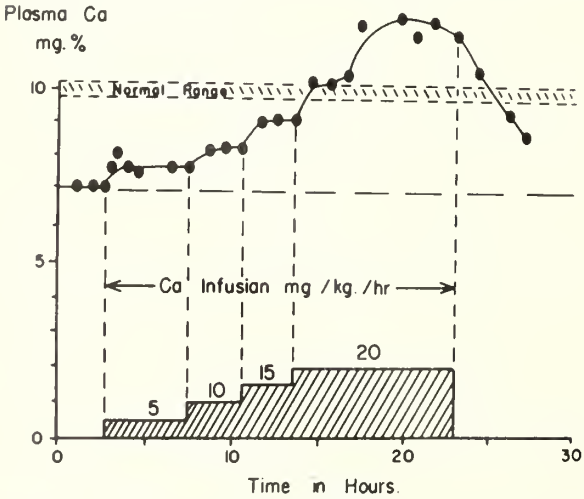

Figure 6.—Result of infusion of calcium at various rates (5, 10, 15 and 20 mg of calcium per kg of body weight per hour) on the plasma calcium level in an eight-week-old parathyroidectomized pig. (Reprinted from Copp[23] with permission.)

In the new steady state the net increase in calcium load is balanced by an increased bone calcium uptake and plasma calcium concentration becomes stable, albeit at a higher level. Parathyroid hormone is not essential for this sequence of adaptive changes, although its absence appears to retard the correction of hypercalcemia to basal calcium concentrations after the discontinuation of the calcium load.

Therefore, the addition of calcium into ECF results in predictable hypercalcemia. This hypercalcemia, however, is promptly stabilized and prevented from escalating by the safety valve action of increased urinary excretion and bone uptake of calcium so that a new steady state is established. Although the kidney ameliorates the burden on bone to buffer the added calcium load and therefore the severity of hypercalcemia, it can also be paradoxically incriminated for sustaining the hypercalcemia by its failure to excrete the entire added calcium load (theoretically, the kidney has the capability of excreting up to about 10 grams of calcium a day).

Figure 5 also illustrates that when parathyroid extract is infused simultaneously with calcium, no equilibrim was achieved during the seven hours of study and that the hypercalcemia failed to resolve promptly after the infusion was discontinued. The effect of bovine parathyroid hormone or extract on calcium homeostasis in man was examined in detail by Froeling and Bijvoet.[32] Part of these authors' study is illustrated in Figure 7. During infusion of the hormone or its extract, an average circulating concentration of 3 ng per ml was maintained and this subsequently took three hours to drop to half the peak concentration. On the other hand, the rate of cyclic AMP excretion synchronized tightly with the initiation and discontinuation of the infusion, suggesting that the renal action of the hormone did not outlast the infusion. If urinary cyclic AMP is a valid index of the quantity of circulating biologically active parathyroid hormone, then the immunoassayable parathyroid hormone detected in serum after cessation of parathyroid hormone infusion must represent the inactive degradation product(s).

Hydroxyproline excretion increased and declined more gradually suggesting that the action of parathyroid hormone on bone outlasts the presence of active hormone in circulation. The development of hypercalcemia was associated with an increase in hydroxyproline excretion (reflecting increased bone resorption) *and* a success-

ful attempt by the kidney not to excrete any of the newly gained calcium (virtual absence of an increase in "cumulative urinary calcium loss"). On the other hand, the correction of the hypercalcemia was associated with a parallel decline in hydroxyproline excretion and an increase in urinary calcium loss. Clearly, the generation and the maintenance of this form of hypercalcemia requires the participation of both bone and kidney.

Parfitt,[25] in his comprehensive review on the action of parathyroid hormone on bone, suggested that clinical hypercalcemia may be considered under two categories: the equilibrium hypercalcemia due to increased activity of homeostatic mechanism which regulates blood-bone equilibrium and the disequilibrium hypercalcemia due to accelerated net bone resorption (Table 1). Lloyd[33] rendered a similar analysis in a group of patients with primary hyperparathyroidism. Most patients with primary hyperparathyroidism have slowly growing adenomas and equilibrium hypercalcemia. The sustained increase in the release of modest amounts of parathyroid hormone results in a proportionate increase in mobilization of calcium from bone into ECF. The calcium concentration in ECF will progressively rise until bone sequestration of calcium once again equals bone calcium mobilization. The resetting of blood-bone equilibrium is paralleled by an increase in renal threshold for calcium so that little or none of the newly gained calcium is lost from the body—much like the experiment depicted in Figure 7. This form of hypercalcemia may be maintained indefinitely without continued loss of calcium from either the bone or the body. A net removal of 150 mg of calcium from bone into ECF and retained by the kidney from excretion would be

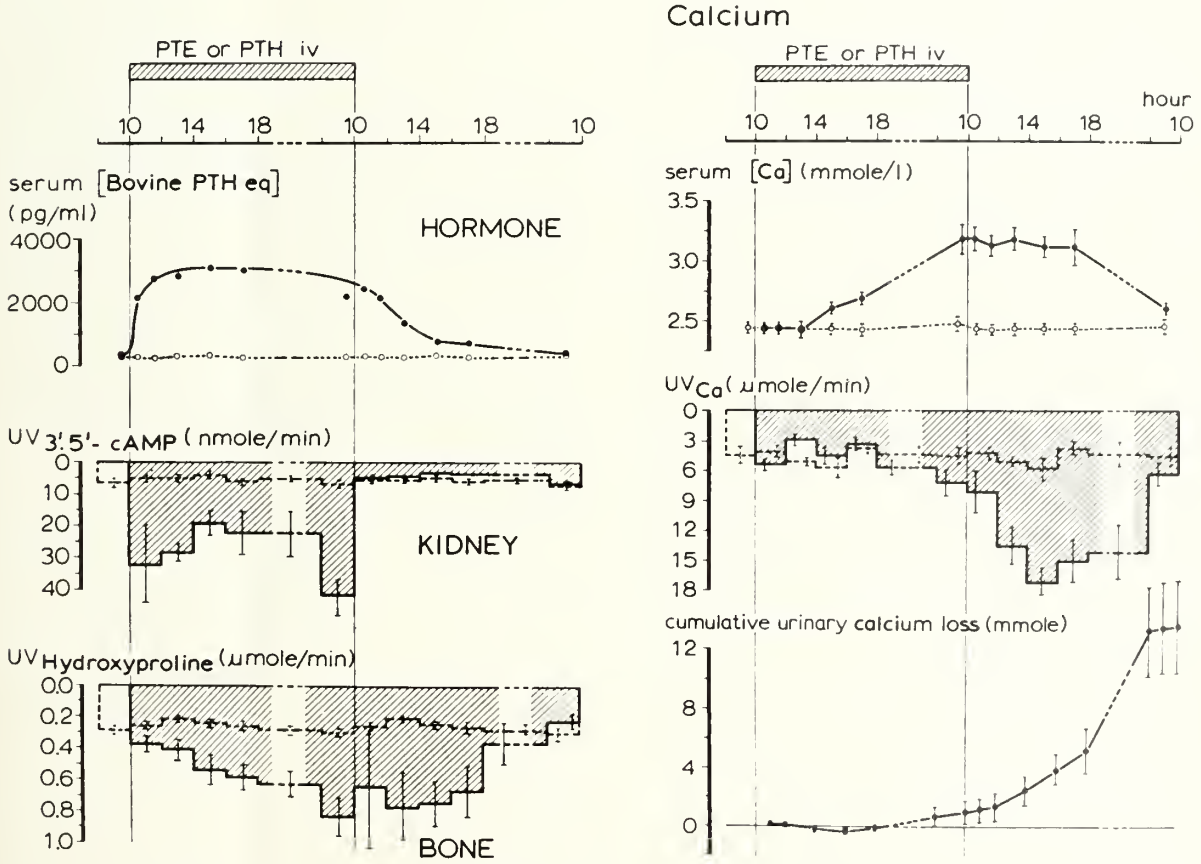

Figure 7.—Effect of continuous intravenous infusion over 24 hours of parathyroid extract (PTE) or parathyroid hormone (PTH) at a rate of 2 USP units per kg of body weight per hour in five persons on: **(left panel)** serum immunoassayable parathyroid hormone and urinary excretion rates of cyclic adenosine monophosphate (UV 3',5'-cAMP) and hydroxyproline; **(right panel)** concentration in the serum, urinary excretion rate and cumulative urinary loss of calcium. Closed circles and drawn lines refer to average ± SEM of measurements on the infusion and the postinfusion day, and open circles and interrupted lines to control measurements in the same persons. (Reprinted from Froeling and Bijvoet[32] with permission.)

TABLE 1.—*Comparison of Equilibrium Hypercalcemia Due to Increased Activity of Homeostatic Mechanism Which Regulates the Blood-Bone Equilibrium with Disequilibrium Hypercalcemia Due to Increased Net Bone Resorption**

Characteristic	*Variety of Hypercalcemia*	
	Equilibrium	*Disequilibrium*
Liability to change	Stable	Unstable
Rate of progression	Slow	Rapid
Size of negative calcium balance	Small	Large
Increase in urinary calcium	Small	Large
Renal failure: incidence	Rare	Common
Renal failure: effect on plasma calcium	Fall	Rise
Response of plasma calcium to corticosteroids	No change	Fall
Lloyd type of primary hyperparathyroidism	II	I

*Reproduced from Parfitt[25] with permission.

adequate to raise plasma calcium by 2 mg per dl. Parfitt calculated that if chronic hypercalcemia of mild, stable hyperparathyroidism were simply an indefinite extension of acute hypercalcemia akin to laboratory infusion studies, then the generation and maintenance of an elevation of plasma calcium by only 1 mg per dl would lead to the total exhaustion of skeletal calcium in seven years.[25] The production of sustained hypercalcemia by simultaneous resetting of blood-bone equilibrium and renal calcium reabsorption (rather than by continuous and unbridled calcium drain from the bone) is also seen in experiments with dogs given chronic low dose (0.2 Medical Research Council units [MRC units] per kg of body weight per hour) of purified parathyroid hormone.[34] Hypercalcemia (maximum rise of 2 to 3 mg per dl) was produced in the absence of elevation of circulating hydroxyproline concentration and bone histology examined after two to three weeks of continuous parathyroid hormone infusion showed no evidence for either osteoclastic or osteocytic resorption. Furthermore, intestinal calcium absorption rose, urine calcium clearance fell and the animals were in fact in positive calcium balance.

In pronounced contrast to the equilibrium hypercalcemia, disequilibrium hypercalcemia is the result of rapid bone resorption or destruction with consequent outpouring of large quantities of calcium into ECF. Renal calcium reabsorption capacity probably becomes rapidly saturated and a large excess of calcium is excreted. Unfortunately, this safety valve function of the kidney may be compromised by the frequent development of renal failure* in hypercalcemias of this kind resulting in further escalation in the magnitude of hypercalcemia. Disequilibrium hypercalcemia may occur in rapidly progressive primary hyperparathyroidism, immobilization, multiple myeloma, metastatic cancer of bone and severe vitamin D intoxication.[25] According to Parfitt,[25] this variety of hypercalcemia may be more responsive to corticosteroid administration.

In clinical practice, the natural history of any given case of hypercalcemia probably consists of a series of alternating equilibrium and disequilibrium phases. In one case, the overall pattern may be predominantly of the equilibrium variety while, in the other, the disequilibrium variety may predominate.

CAUSES OF HYPERCALCEMIA ENCOUNTERED IN CLINICAL PRACTICE

Experience at the University of California, Los Angeles

At the University of California, Los Angeles, Medical Center, from April 1, 1975, to March 31, 1976, a total of 184 patients were found to have one or more serum calcium determinations equal to or exceeding 11.0 mg per dl. Figure 8 illustrates the breakdown of these cases into age groups. About 40 percent of the total cases were found in patients in the first two decades of life. With the exception of one case of primary hyperparathyroidism, no apparent cause for hypercalcemia was documented in the remaining 70 patients. The most likely explanation for this interesting finding is the phenomenon known as physiological hypercalcemia which will be further discussed in later sections. Causes or associated conditions were identified in 80 patients and are depicted in Figure 9. Malignancy clearly leads the

*The role of renal calcium excretion in regulating the severity of a given hypercalcemic state is also suggested by the recent experimental work of Weisbrode and Capen.[35]

list as a cause of hypercalcemia followed by primary hyperparathyroidism. This is in conformity with experience from other studies in patients in hospital.[36-38] The "recent calcium load" category consists mainly of subjects who have previously received calcium during cardiac surgical operations or cardiac resuscitation. A few remaining patients were receiving parenteral hyperalimentation or calcium infusion for diagnostic purposes. The five patients who manifested hypercalcemia while receiving thiazide therapy may have had primary hyperparathyroidism (vide infra) but the diagnosis was not conclusively established. Of the patients in whom hypercalcemia developed while receiving hemodialysis therapy or after renal transplantation, none were receiving vitamin D or supplemental calcium and the hypercalcemia was attributed to parathyroid hyperplasia or "tertiary hyperparathyroidism." In the two patients who had hypercalcemia associated with bone disease, one had histiocytosis and the other had Paget disease. Figure 10 depicts the distribution, according to age groups of patients, of two hypercalcemic syndromes diagnosed most frequently in our hospital. Both conditions almost exclusively afflict the older age groups. Primary hyperparathyroidism characteristically occurs most frequently in the fifth decade, while the number of malignancy-associated hypercalcemic cases dramatically increases in the fourth decade and thereafter continues as the predominant cause of hypercalcemia encountered in hospital practice.

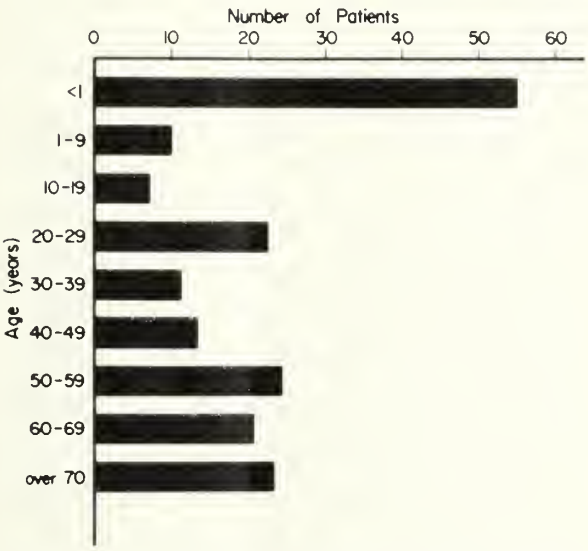

Figure 8.—Age distribution of patients with hypercalcemia seen at the University of California, Los Angeles, Medical Center from April 1975 to March 1976.

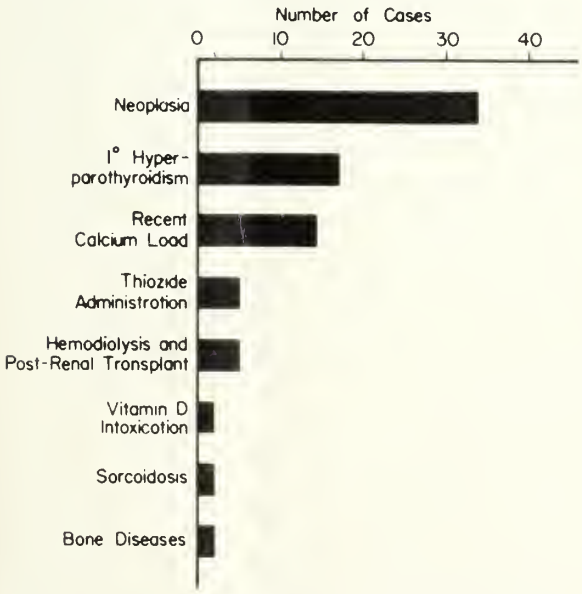

Figure 9.—Causes of hypercalcemia encountered at the University of California, Los Angeles, Medical Center from April 1975 to March 1976.

The proportion of primary hyperparathyroidism as a cause of hypercalcemia increases and that of malignancy decreases as the studied population becomes less selective. Therefore, in the 67 patients with abnormal serum calcium concentrations detected by routine analysis in 25,847 persons seen consecutively at a general medical clinic, about half had hyperparathyroidism and a quarter had malignancies.[39] In 15,903 subjects who accepted invitation to a health check service, 95 had hypercalcemia confirmed by repeated testing.[40] Of these 95 patients, only two had malignancies. Hyperparathyroidism was suspected in 88 patients of whom 59 had neck exploration by the time of reporting and 57 had parathyroid

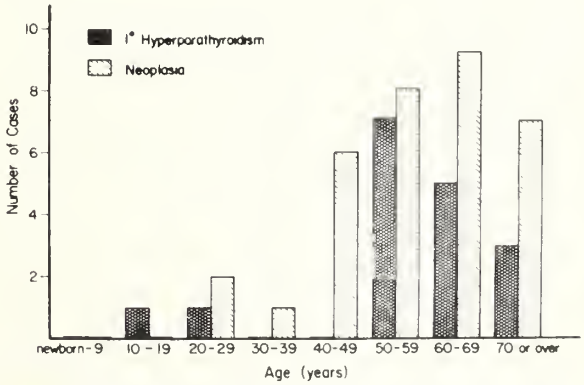

Figure 10.—Age distribution of patients with primary (1°) hyperparathyroidism and neoplasia hypercalcemia seen at the University of California, Los Angeles, Medical Center from April 1975 to March 1976.

TABLE 2.—*Causes of Hypercalcemia*

1. Neoplasms
   - Skeletal metastases
   - Increased production of parathyroid hormone (PTH) or PTH-like factors
     - Coexistent hyperparathyroidism
     - Ectopic PTH secretion (pseudohyperparathyroidism)
   - Non-PTH hypercalcemic factors
     - Osteolytic phytosterols
     - Prostaglandins
     - Osteoclast activating factors
     - Vasoactive intestinal peptides (VIP)
   - Neoplasm-related complications
     - Dehydration
     - Acute immobilization
     - Therapeutic agents: estrogens, androgens, progestins, tamoxifen
     - Adrenal insufficiency secondary to tumor metastases
     - Hyperproteinemia

2. Hyperparathyroidism
   - Primary hyperparathyroidism
     - Idiopathic
     - Familial
     - Association with:
       - Extraparathyroid neoplasia
       - Thyrotoxicosis
       - Multiple endocrine abnormalities
   - Hypercalcemic secondary hyperparathyroidism
     - Renal failure:
       - Acute
       - Chronic
     - Post-renal transplant
     - Osteomalacia associated with malabsorption
     - Postresection of bone or soft tissue tumors associated with vitamin D resistant osteomalacia/rickets

3. Nonparathyroid endocrinopathies
   - Hyperthyroidism
   - Hypothyroidism
   - Hypoadrenocorticism
   - Pheochromocytoma
   - Acromegaly

4. Pharmacological agents
   - Vitamin D and its metabolites
   - Vitamin A
   - Milk-alkali syndrome
   - Thiazide diuretics
   - Calcium
   - Lithium

5. Possible increased sensitivity to vitamin D
   - Granulomatous disease: sarcoidosis, tuberculosis, histoplasmosis, coccidioidomycosis
   - Idiopathic infantile hypercalcemia

6. Miscellaneous
   - Physiological hypercalcemia
   - Immobilization
   - Other hypercalcemic conditions in children
   - Acute renal failure, usually associated with rhabdomyolysis
   - Chronic renal failure
   - Phosphorus depletion in uremic patients
   - Hypophosphatasia
   - Generalized periostitis

adenomata. In both series, subjects older than 40 years constituted the bulk of the population studied.

Selected aspects of the various causes of hypercalcemia (Table 2) encountered in clinical practice will now be discussed.

Neoplasia

Neoplastic disease, as previously discussed, is probably the most common cause of hypercalcemia encountered in hospital practice. The malignancy most frequently complicated by hypercalcemia is breast cancer. Elevated serum calcium concentrations in this disease are usually associated with skeletal metastases, although the severity of hypercalcemia is not necessarily correlated with the extent of metastatic bone destruction. Therefore, some women with extensive skeletal metastases never become hypercalcemic, while in others with apparently no bone involvement pronounced hypercalcemia developed.[41] In from 7 percent[42] to 25 percent[43] of patients with breast cancer hypercalcemia may develop, sometimes precipitated by hormone therapy.[41,44] Thomas and associates[45] detected hypercalcemia in 42 percent of their breast cancer patients at some stage of the disease, and other workers have reported similar findings.[46,47]

Of the tumors which frequently cause hypercalcemia in the absence of bone involvement,* cancer of the lung and renal cell carcinoma top the list.[49,50] Bender and Hansen[51] found that in 12.5 percent of 200 patients with lung cancer hypercalcemia developed at some stage of their disease. This complication was found predominantly associated with epidermoid and large cell anaplastic-cancer, but was uncommonly associated with adenocarcinoma and oat cell carcinoma, the two cell types most frequently associated with skeletal metastases. In a group of 118 patients with renal cell carcinoma, Warren and associates[52] found 15 (13 percent) instances of hypercalcemia before the operation. Several other reviews have summarized different types of cancer causing hypercalcemia of malignancy.[49,50,53-56]

The mechanism of intraskeletal tumor-induced bone resorption is not clear. Direct pressure effect and local release of chemical and hormonal sub-

*Normal radiographs do not necessarily exclude the presence of skeletal metastases. Bachman and Sproul,[48] in an autopsy series, documented that only 50 percent of cases with histologically demonstrable osseous metastases had radiographic findings suggestive of metastatic cancer. Increased diagnostic yield may be achieved by the additional use of other procedures such as bone biopsy, marrow aspiration and bone scanning.

stances by tumor are some of the postulated factors. These substances include hydrogen ions, citrates, osteoclast activating factors and prostaglandins, some of which will be discussed in the following sections.

Hypercalcemia of malignancy may sometimes be associated with an increased concentration of radioimmunoreactive parathyroid hormone (PTH) in blood. This increase in PTH may result from a parathyroid adenoma coexistent with the malignancy, vide infra, or more often, the inappropriately high PTH or PTH-like substance is produced by the tumor tissue. The concept of parathyroid hormone secretion by neoplastic tissue was first proposed by Albright[57] in 1941. Although a number of subsequent studies greatly substantiated the original concept by indirect evidence,[49,50] it was not until the advent of PTH measurement that Albright's suggestion was confirmed. It is now clear that in some patients with nonparathyroid neoplasm, hypercalcemia may develop without osseous metastases and in association with increased quantities of PTH in the circulation,[58-64] the tumor tissue,[58,59] or in the tumor effluent blood.[59] Ectopic PTH production by breast cancer is considered rare[65] although in one report all 14 patients with breast cancer and hypercalcemia had elevated serum levels of immunoreactive PTH.[65a] More recently, ectopic parathyroid hormone production has also been described in association with acute lymphocytic and myeloblastic leukemias[66-68] and acute myelofibrosis.[69] The finding of elevated PTH in malignancy-associated hypercalcemia, however, should not automatically lead to a cause and effect conclusion. Berson and Yalow have documented the elevation of PTH levels in blood in a significant proportion of patients with cancer of the lung in whom hypercalcemia was absent.[60] This is understandable since the biologic implications of various circulating PTH fragments are still not fully appreciated. It has also been shown that neoplasms may produce other polypeptides devoid of biologic activities.[70,71] Furthermore, the specificity and the sensitivity of various antibodies used by different laboratories in the measurement of parathyroid hormone remain to be rigorously standardized.[72] What is clear, however, is that not all neoplasms, without osseous metastases, produce hypercalcemia by ectopic production of PTH.

In a study of 11 patients with tumor-associated hypercalcemia, hypophosphatemia and the absence of obvious skeletal metastases, Powell and associates were unable to show the presence of PTH by multiple immunoassay techniques designated to measure intact hormone as well as precursors and fragments in both plasma samples and tumor tissues.[73] These authors concluded that humoral factor(s) other than PTH may be responsible for the development of hypercalcemia. The conclusion was further supported by their observation that non-PTH-containing extracts from tumors in five patients caused active bone resorption *in vitro,* and that the hypercalcemia in these patients regressed with specific antitumor therapy.

Several non-PTH, hypercalcemic factors have been reported. Gordan and co-workers have identified phytosterols, which caused osteolysis in rats, from the plasma and tumor tissue of patients with breast cancer and hypercalcemia in the absence of skeletal metastases.[74] However, this observation and its significance still require confirmation.[75]

The suggestion that prostaglandins may be important in the genesis of hypercalcemia associated with neoplasia is based on the observations that prostaglandins of the E series (PGE) are potent stimulators of bone resorption *in vitro.*[76] PGE_2 is most probably the bone resorption-stimulating factor responsible for the hypercalcemia seen in transplantable mice fibrosarcoma $HSDM_1$[77] and rabbit carcinoma VX_2.[78] The possible role of prostaglandins as mediators of hypercalcemia caused by malignancy in man has been reported in renal cell carcinoma,[79-81] breast cancer,[82] parotid-gland carcinoma[83] and a variety of other solid tumors including carcinoma of the lung, adenocarcinoma of the pancreas and metastatic adenocarcinoma of unknown origin.[84] It is estimated that about a third of the patients with hypercalcemia, neoplasia and normal serum parathyroid hormone levels had hyperprostaglandinemia (quoted in reference 85). Horrobin[86] suggested that prostaglandin production by metastases of breast cancer in bone may be regulated by prolactin and this may account for the relief of bone pain achieved by the use of prolactin-suppressive drugs. Seyberth and associates identified prostaglandin-dependent, cancer-associated hypercalcemia by measurement of the major urinary metabolite of the E prostaglandins, PGE-M. In patients with increased urinary excretion of PGE-M (indicating increased prostaglandin E production), treatment with aspirin or indomethacin was followed by improvement or resolution of hypercalcemia associated with a parallel decrease in urinary excretion of

PGE-M.[84] The greatest reduction in serum calcium is seen in high PGE-M excreters without bone metastases. In another series of hypercalcemic patients with malignancy, hyperprostaglandinemia was found in four of 11 patients.[87] Serum calcium levels were lowered by prostaglandin-inhibitors only in those patients with hyperprostaglandinemia before treatment. On the other hand, Ito and associates[81] found a decreased sensitivity of patients with neoplasia-hypercalcemia to the calcium-lowering action of indomethacin on repeated administration. Dindogru and co-workers[88] documented an inconsistent effect of indomethacin in five patients with hypercalcemia. PGE also does not consistently produce hypercalcemia in different strains of animals.[89-92] More recently, Robertson and Baylink[93] suggested that failure to induce hypercalcemia in intact rats during PGE_2 infusion may be due to calcitonin counterregulation. Therefore, although there is now increasing circumstantial evidence incriminating hyperprostaglandinemia as a cause of hypercalcemia in some patients with cancer, the precise interrelationship between prostaglandins and calcium metabolism is still not clearly understood.[94] The use of prostaglandin inhibitors as a therapeutic modality for tumor hypercalcemia, at present, should be considered experimental and monitored carefully.[95-97]

When normal human leukocytes are stimulated by antigens or phytomitogens *in vitro,* yet another bone resorbing factor different from PTH, vitamin D-like substance or prostaglandins may be released into the culture medium. This substance was named osteoclast activating factor (OAF) and was thought to play a role in the local bone resorption seen in periodontal disease, arthritis and osteomyelitis.[98-100] Mundy and co-workers have shown a factor similar to an OAF produced by human myeloma[101] and lymphoma[102] cells cultured *in vitro.* Examination of bone samples from the same group of patients showed osteoclasts on bone-resorbing surfaces adjacent to areas of heavy myeloma-cell infiltration. These authors therefore suggested that the osteolytic bone lesions and hypercalcemia seen in patients with myeloma may be secondary to the secretion of an OAF by the myeloma cells. Recently, direct bone resorption by human peripheral monocytes *in vitro* has also been demonstrated in two laboratories.[103,104] However, the question of whether such resorption requires a direct contact between the cells and the resorption surface and whether the resorption also requires the transformation of these monocytes into osteoclast-like cells remains unsettled.

Verner and Morrison[105] first described the syndrome of copious watery diarrhea, hypokalemia and non-β islet cell tumor of the pancreas. Patients with this syndrome often have elevated serum levels of vasoactive intestinal peptide (VIP)[106] or PGE, or both.[107] Hypercalcemia has been reported in a number of these cases.[85,108-110] Although the exact relationship between VIP and hypercalcemia remains to be elucidated, there is now preliminary experimental[111] and clinical[108] evidence suggesting a direct action of VIP on bone resorption and induction of hypercalcemia.

In dealing with tumor related hypercalcemia, it is also important to bear in mind that, frequently, the magnitude of hypercalcemia is exaggerated or may even be entirely accounted for by indirectly related factors such as immobilization, dehydration, the development of adrenal insufficiency from tumor metastases[112,113] and the use of therapeutic agents including estrogens, androgens and progestins.[41,44] (More recently, tamoxifen, an antiestrogenic agent used in the treatment of breast cancer, has been reported to cause hypercalcemia [Ann. Intern. Med. 88:574-575, 1978].) Baker estimated that two thirds of hypercalcemia seen in patients with breast cancer was induced by sex steroid administration.[114] The basic mechanism is unclear, but sex hormone-induced escalation of intraskeletal tumor growth and claboration of possible calcium mobilizing factors have been postulated.[54] Recent interest in the interaction between sex steroids and vitamin D metabolism[115-117] may potentially lead to further information on this interesting phenomenon. Of interest also is the observation that mammary glands may have a specific vitamin D-binding protein which has greater affinity for vitamin D than the serum-binding protein.[118] Finally, in patients with hyperproteinemia, an increase in the protein-bound fraction of plasma calcium may be responsible for the observed hypercalcemia.[8,112]

Hyperparathyroidism

Primary Hyperparathyroidism

Primary hyperparathyroidism (PHPT) is probably the most common cause of hypercalcemia in unselected populations.[39,40] When serum calcium concentration is measured on a routine screening basis, the incidence of PHPT ranged from 0.1 percent[39] to 0.36 percent.[40] The former figure was

obtained from screening 25,847 patients consecutively seen at a general medical clinic in the United States and the latter figure was obtained from a free health check survey of 21,417 employees of the Stockholm City and County Council.

PHPT occurs twice as frequently in females as in males.[33,40] The incidence of the disease is at its highest from the fourth to the sixth decades, mainly as a result of the dramatic increase in the number of female patients (Figure 11). In man, PHPT appears to occur with equal frequency from the third to the seventh decades. The development of PHPT is infrequent at the extremes of age groups and when it does occur, it usually afflicts the females (Figure 11). PHPT in infancy and the neonatal period[119-121] should be differentiated from parathyroid hyperplasia secondary to untreated maternal hypoparathyroidism.[122] A familial association is usually demonstrable in infant and neonate PHPT. Familial hyperparathyroidism is the subject of several recent articles.[123,124] Pregnancy may exacerbate hyperparathyroidism which has been reported to result in an increased incidence of spontaneous abortion, perinatal and neonatal death, and prematurity.[125]

There are no known factors to which the development of PHPT can be clearly attributed. In normal subjects, the weight of parathyroid glands increases until the third decade in men, but continues to increase until the fifth decade in women.[126] Lloyd[33] reasoned that the greater the mass of normal tissue, the greater may be the risk of neoplastic change, thereby accounting for the

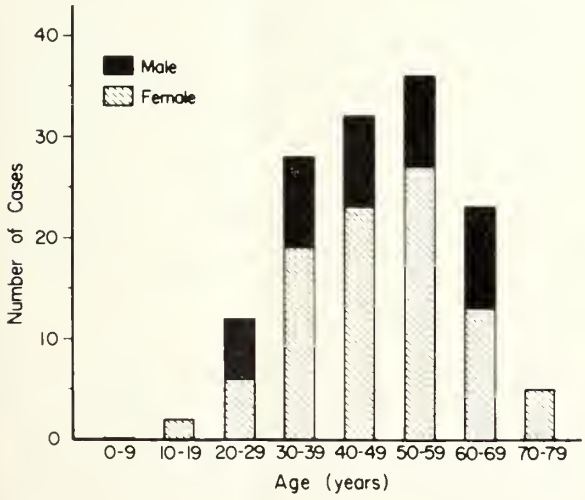

Figure 11.—Distribution of cases of primary hyperparathyroidism according to age in decades [data derived from Lloyd[33]].

increase in the incidence of parathyroid tumor in older women but not in older men. However, it is now well known that adenomatous change of secondary hyperparathyroidism is distinctly uncommon, if it occurs at all, vide infra. Recently, the possible role of previous neck irradiation in the development of hyperparathyroidism has been raised.[127,128] In one study, 20 of 69 consecutively seen patients with surgically proven hyperparathyroidism had a history of previous irradiation to the head and neck area.[128]

Pathologically, more than 80 percent of the cases of PHPT are accounted for by adenomas, 15 percent by hyperplasia and slightly less than 5 percent by carcinoma.[33,129,130] However, some workers claim that the incidence of single adenoma and chief-cell hyperplasia in patients with PHPT is about equal.[131] The apparent disagreement may be attributed to the recognized lack of conclusive pathological criteria for differentiating adenomas from hyperplasia. For this reason, Block and associates used the terms single-gland and multiple-gland involvement rather than adenomas and hyperplasia.[132] Fialkow and co-workers,[133] in a novel study of four parathyroid gland adenomas in three women with heterozygosity for X-linked enzyme glucose-6-phosphate dehydrogenase, advanced evidence for the multicellular origin of parathyroid adenomas. They postulated that these adenomas probably evolved from initial hyperplasia and thus further enhanced the similarities between adenomas and hyperplasia. Clinical aspects of parathyroid carcinoma were reviewed by Schantz and Castleman[134] in a study of 70 cases. Rare cases of functioning lipoadenoma of the parathyroid gland have also been reported.[135]

The natural history of PHPT may vary from a relatively benign, nonprogressive course[136-138] to an acute catastrophe characterized by fulminant and, frequently, fatal hypercalcemia.[139-141] Spanning these two extremes are the more classical cases of hyperparathyroidism with bone and stone disease. Lloyd,[33] on the basis of careful analysis of clinical data on 138 patients with PHPT, suggested that parathyroid tumors may be segregated into two varieties, one characterized by rapid growth, "high activity" and overt bone disease, and the other characterized by slow growth, "low activity" and kidney stones. Farr[142] pointed out that not only has the incidence of hyperparathyroidism sharply increased with the routine use of SMA-12 analysis, but the pattern of clinical pre-

sentation has also noticeably changed. In the early years, the parathyroid tumors averaged 3 to 5 cm and were often palpable before surgical operation. Skeletal and renal manifestations were frequent. In recent years, adenomas averaged 1 to 2 cm in size and symptoms were often minimal—in almost half of the patients diagnosis was made because of the laboratory finding of hypercalcemia but the patients were otherwise asymptomatic. In a number of patients with hyperparathyroidism, hypercalcemia was masked by superimposed vitamin D deficiency as a consequence of simple vitamin D deficiency,[143,144] malabsorption[145] and the administration of anticonvulsants.[146]

Boonstra and Jackson[39] pointed out that 23 of 31 patients initially considered asymptomatic, in fact had nonspecific symptoms such as fatigue and nervous irritability which became apparent only after their alleviation following excision of the parathyroid adenoma. Neuromuscular dysfunction, often blamed by patients on aging, has also been emphasized by Patten and associates.[147] St. Goar[148] originally suggested that hyperparathyroidism may be remembered as a disease of "stones, bones and abdominal groans" to which Mieher, Thibaudeau and Frame[149] added "and psychic moans." Boonstra and Jackson[39] rightly updated the statement to "stones, bones, abdominal groans, psychic moans and fatigue overtones."

A recent surge of interest in PHPT has also uncovered or reemphasized some other less widely known features of the disease. Aurbach and associates stressed the relatively high prevalence of weight loss, arthralgias, anemia and elevated erythrocyte sedimentation rate in patients with uncomplicated PHPT.[150] Falko and associates[151] found that the association between anemia and PHPT occurs, but is unusual. On the other hand, Boxer and co-workers[152] found an association rate of 5.1 percent. When anemia does occur, its mechanisms are obscure but it generally reverses with appropriate surgical therapy. About 20 percent to 50 percent of patients with PHPT have hypertension[153-156] and it is estimated that 1 percent of the hypertensive population may have PHPT.[155] Christensson and associates[157] showed a consistently higher blood pressure (not necessarily at hypertensive levels) in a series of asymptomatic, hypercalcemic, hyperparathyroid patients when compared to age-matched and sex-matched normocalcemic controls. Dauphine, Riggs and Scholz[158] recently drew attention to another less emphasized mode of presentation for primary hyperparathyroidism: back pain and vertebral crush fractures in the absence of unequivocal x-ray evidence for hyperparathyroid bone disease. The clinical implication of this observation is abundantly clear, since symptomatically and roentgenographically these patients are indistinguishable from patients with postmenopausal osteoporosis—a population in which PHPT also has its peak incidence.

Concerning peptic disease, Christensson, Hellström and Wengle[40] found no difference in the occurrence of gastritis or peptic ulcer (or both) between patients with PHPT discovered through mass health screening and age-matched and sex-matched controls. McGeown and Connell[159] reported that although there is a high incidence of dyspepsia and duodenal ulcer in patients with PHPT, they do not have increased acid secretion. For interested readers, a list of other reported associations follows: gout,[160] pseudogout,[161] ankylosing spondylitis,[162] sarcoidosis,[163] cholelithiasis,[164] pancreatitis,[165] and depression and psychosis.[166,167] Alteration in insulin metabolism in the absence of overt defect in glucose tolerance has also been documented.[168,169] Rao and co-workers[170] pointed out that in some patients with medullary sponge kidney, the cause of nephrolithiasis may be an associated parathyroid adenoma and, therefore, should not always be summarily attributed to underlying anatomic abnormality.

The interrelationship between PHPT and extraparathyroid neoplasia has been noted by a number of investigators. In a series of 100 patients reviewed by Farr,[142] extraparathyroid malignancy was found before, during or after the removal of a benign parathyroid tumor in as many as a third of the patients. Stomach and breast cancer were the most common associated neoplasms, followed by cancer of the skin, colon and thyroid. Kaplan and associates reviewed the cases of 166 patients with histologically proven parathyroid adenoma—in 104 patients shown at surgery and in 62 patients at autopsy.[171] Part of the data from this exhaustive work is summarized in Figure 12. It can be seen that in patients with clinically diagnosed and confirmed parathyroid adenoma, no less than 16 percent have coexistent extraparathyroid neoplasia. In female patients, the incidence goes up to to 23 percent. In 62 patients with parathyroid adenoma in whom autopsy studies were done, almost half had nonparathyroid ma-

lignancy. In all except two patients, parathyroid adenoma was not suspected before death. Premortem data such as the presence or absence of hypercalcemia were not available. It is likely that hypercalcemia may have been present and may have contributed to the morbidity and final demise of a number of these patients. In both the surgical and autopsy series, the most common extraparathyroid neoplasias were those involving the breast, thyroid, and gastrointestinal tract and appendages. The coexistence of PHPT with breast cancer,[172,173] nonmedullary cancer of the thyroid[174,175] and renal cell cancer[176] has also been documented by others. Nemoto and associates[177] reported a case of PHPT associated with triple cancers involving kidney, nasopharynx and thyroid.

The finding of concomitant nonparathyroid neoplasia in surgically proven primary hyperparathyroidism was also reported by Johansson and Werner[178] from Sweden. The rate of such association, however, was lower (13 instances out of 350 cases, or 4 percent) and the types of neoplasia were of a different pattern. There was a preponderance of disorders affecting marrow activity and globulin synthesis such as multiple myeloma and polycythemia. The series had only one case of thyroid cancer and no cases of breast cancer or cancer of the gastrointestinal tract and its appendages. The reason for the impressive difference between different series reported from different geographical areas is not clear. What is

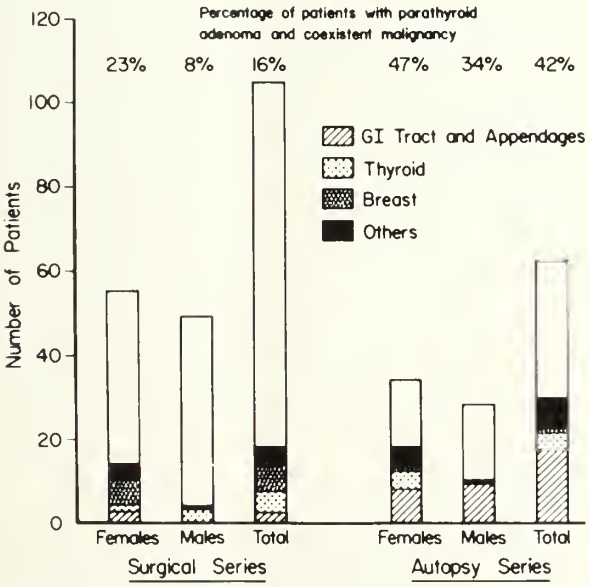

Figure 12.—Coexistence of malignant neoplasms and parathyroid adenoma [data derived from Kaplan et al[171]].

reasonably certain is that PHPT and neoplasia may coexist more frequently than could be expected by chance. The mechanism for this association is entirely unknown. One might speculate about the existence of a common etiologic process or agent which causes sustained and functional aberrations in both the parathyroid gland and the extraparathyroid tissue. Alternatively, either the nonparathyroid tumor may produce a parathyroid-trophic agent which results in the development of hyperparathyroidism or, conversely, PHPT may lead secondarily to an aberrant cellular and subcellular process and the development of neoplasia in extraparathyroid tissue. Clubb and associates described a hyperparathyroid patient with coexistent serum "paraprotein." The paraprotein disappeared after parathyroidectomy.[179] The association between cancer and hyperparathyroidism is, however, not a universal observation. Aurbach and associates,[150] in a series of 100 cases of PHPT, reported no occurrence of extraparathyroid neoplasia. However, interestingly, they noted an unexpectedly high prevalence of weight loss, anemia, and elevated sedimentation rate in their patients. It is possible that this series may consist predominantly of patients who received earlier referral, diagnosis and treatment. Data on further follow-up of these patients will therefore be of considerable interest and importance.

For the moment, the interrelationship between PHPT and neoplasia should still be considered empirical. From the clinical standpoint, however, it is important to be aware of the association so that under circumstances which warrant suspicion, the diagnosis of one disease should lead to attempts at uncovering the other. For example, the discovery and removal of a parathyroid adenoma in patients with neoplasia and hypercalcemia may lead to gratifying correction or amelioration of hypercalcemia and other related symptoms which otherwise would have been wrongly blamed on the progression of the underlying neoplastic process.

PHPT may also coexist with other endocrine disorders. The association may involve the dysfunction of another gland, such as with thyrotoxicosis,[180,181] or multiple glands generally known as the multiple endocrine adenomatosis syndromes (MEA).[182] In MEA I,[183] hyperplasia, adenoma or carcinoma of one or more endocrine glands is inherited by autosomal dominant transmission. The parathyroids, pancreatic islets and pituitaries are most commonly affected. Some investigators

consider also the inclusion of bronchial,[184] thymic[185] and small bowel[186] carcinoids in the MEA I spectrum. Although the Zollinger-Ellison (ZE) syndrome is generally considered to represent a variation of MEA I, some workers suggest that the evolution of hyperparathyroidism in patients with this syndrome is secondary rather than primary in nature.[187] Malabsorption, presence of circulating calcium-lowering polypeptides and metabolic alkalosis (secondary to persistent gastric hypersecretion, vomiting and antacid ingestion) have all been proposed as possible parathyroid gland stimulants in this condition, leading to secondary hyperparathyroidism. The observation that pathologically the parathyroid glands in patients with gastrinomas frequently show chief cell hyperplasia or multiglandular involvement[188] is also taken as evidence for secondary hyperparathyroidism.

MEA II denotes the combination of pheochromocytoma, hyperparathyroidism and medullary thyroid carcinoma. This syndrome is also inherited in an autosomal dominant pattern. About 15 percent of family members manifest overt disease, and, of these, approximately half have pheochromocytoma only.[189] MEA III or MEA IIb include medullary carcinoma of the thyroid, pheochromocytoma, mucosal neuromas and marfanoid features.[190] Medullary carcinoma is almost always present and pheochromocytoma is less common in MEA III, whereas in MEA II, pheochromocytoma is about twice as common as medullary thyroid carcinoma. Also, hyperparathyroidism almost never occurs in MEA III but develops in half of all affected family members with MEA II. The distinction between the phenomenon of multiple endocrine neoplasia and that of ectopic hormone production was discussed recently by Metz.[191]

Hypercalcemic Secondary Hyperparathyroidism

Secondary hyperparathyroidism almost always results from disease states characterized by reduction in blood concentration of ionized calcium. More recently, secondary hyperparathyroidism has also been reported in conditions with augmented urinary calcium excretion in the absence of discernible hypocalcemia. These conditions include idiopathic hypercalciuria[192,193] and distal (type 1) renal tubular acidosis.[194,195]

The most frequent cause for secondary hyperparathroidism encountered in clinical practice is renal failure, both acute[196] and chronic.[197] Hypercalcemia may develop in both varieties of renal failure, either as a result of or independently from secondary hyperparathyroidism. In acute renal failure, hypercalcemia may develop during the diuretic phase, especially in patients with rhabdomyolysis.[198-201] The pathogenesis of the hypercalcemia is not clear. Postulated mechanisms include remobilization of previously deposited calcium in the damaged muscle, transient hyperparathyroidism and immobilization. In chronic renal failure, hypercalcemia may develop in some patients with so-called "overt," "tertiary" or "autonomous" secondary hyperparathyroidism.[197] In rare instances, hypercalcemia represents one manifestation of the syndrome of calciphylaxis in man.[202] Other causes of hypercalcemia in patients with chronic renal failure include excessive administration of vitamin D and its metabolites,[203-205] large doses of oral calcium carbonate therapy,[206] high dialysate calcium concentration,[207] phosphorus depletion,[197,208,209] immobilization,[210] and the administration of calcium resins[211,212] or thiazides (see section on thiazide diuretics and hypercalcemia).

Rapid correction of chronic uremia by successful renal transplantation may sometimes result in the development of acute and severe hypercalcemia (greater than 13 mg per dl) necessitating emergency subtotal parathyroidectomy for salvaging graft function.[213,214] More frequently, post-transplant hypercalcemia is milder (less than 12 mg per dl) and may persist for years after successful transplantation.[21,215-217] This form of hypercalcemia is generally attributed to a slow and incomplete resolution of parathyroid hyperplasia. Adenomatous transformation is extremely rare.[218,219] Other postulated mechanisms include mobilization of metastatic calcifications and hypophosphatemia.[213,214,220] The effect of chronic low-grade hypercalcemia on transplant function is uncertain. Giess and associates reported evidence suggestive of an adverse effect[21] while others failed to show similar evidence.[214,215]

Finally, adenomatous transformation of secondary hyperparathyroidism has been reported in cases of patients with osteomalacia associated with intestinal malabsorption[221-224] "Tertiary" hyperparathyroidism is also suspected, but not proven, to play a role in the development of hypercalcemia following removal of bone or soft tissue tumors associated with vitamin D resistant osteomalacia or late onset rickets.[225-227] The possible development of "autonomy" in secondary hyperparathyroidism associated with hypercal-

ciuria has also been postulated in renal tubular acidosis[195] and idiopathic hypercalciuria.[193]

Nonparathyroid Endocrinopathies

Hyperthyroidism

The association between hyperthyroidism and increased serum calcium concentration is well known.[22,228-234] In a recent study of 45 hyperthyroid patients, elevated ionized and total calcium concentrations were shown in 47 percent and 27 percent, respectively, of the patients.[22] No correlation was found between the level of serum calcium and the level of circulating thyroid hormone.[228,231] Calcium metabolic studies showed increased urinary calcium (at times as great as 1 gram in 24 hours [personal observation by CRK]), decreased intestinal absorption of calcium and a negative calcium balance.[235] Hypercalciuria, often in the absence of hypercalcemia, may be due to parathyroid hormone suppression induced by increased calcium release from bones, which probably also accounts for the tendency towards higher serum phosphorus levels and decreased renal phosphate clearance in hyperthyroidism.[236] The presence of hypophosphatemia in thyrotoxicosis suggests coexisting hyperparathyroidism. Study of bone metabolism in hyperthyroid patients shows increased bone remodeling activities. Both active bone resorption surface and osteocytic osteolysis are increased, associated with a significant but less pronounced increase in bone formation surface. The changes in bone cells are similar to those seen in hyperparathyroidism including periosteal bone erosion with mononucleated osteoclasts.[234] Mosekilde and associates[237] consider the increase in osteoclastic activity in cortical bone the most striking skeletal change in hyperthyroidism. They noted that this measurement is positively correlated with serum concentrations and urinary excretion of calcium and phosphorus.

Although the incidence of hyperparathyroidism is increased in thyrotoxic patients when compared with the euthyroid population,[180] the development of hypercalcemia in hyperthyroid patients is usually associated with normal or low levels of parathyroid hormone.[22,231,236,238-240] Thyroid hormone has been shown to increase serum calcium levels in hypoparathyroid states[241,242] and successful antithyroid therapy results in resolution of thyrotoxic hypercalcemia.[243] The possible role of calcitonin in the changes in calcium and phosphorus metabolism in hyperthyroidism has also received attention. Thyroxine administration in rats is known to reduce thyroid content of calcitonin.[244] The hypocalcemic effect of a given amount of calcitonin is exaggerated in hyperthyroid patients when compared with normal subjects.[245] Several authors have postulated that an absolute or relative lack of calcitonin may be responsible for the observed disturbances in divalent ion metabolism.[231,240,246,247] The possibility that thyroxine may potentiate the effect of vitamin D has been raised by those experienced in the treatment of hypoparathyroidism with vitamin D or dihydrotachysterol. Hypoparathyroid patients with concomitant hypothyroidism often have considerable resistance to treatment with vitamin D or dihydrotachysterol. Administration of thyroxine to such patients results in a notable increase in their response and sensitivity to vitamin D.[234] More recently, Pavlovitch, Presle and Balsan[248] have clearly shown that, in rats, selective thyroid depletion decreases the sensitivity of bone to the calcemic effect of 1,25-dihydroxycholecalciferol. The recent report of symptomatic hypercalcemia in two thyrotoxic patients responding to treatment with propranolol opens the way to yet another hypothesis.[249] An increase in beta-adrenergic activities or an increase in skeletal responsiveness to circulating beta-adrenergic agents (or both) is postulated in thyrotoxicosis. Beta-adrenergic agonists have been shown to raise cyclic AMP in bone cultures.[250]

Hypothyroidism

Hypercalcemia is an infrequent complication of cretinism and myxedematous states.[31,251] Hypothyroidism is characterized by a profound decrease in bone remodeling activities. The cancellous bone volume is, however, increased, indicating that although bone remodeling is reduced, the balance of bone cell activity favors bone formation.[252] Intestinal calcium absorption is increased and the calcium balance is positive.[234] The pronounced reduction in bone turnover rate may lead to a reduction in the normal skeletal "buffering" capacity for calcium homeostasis (refer to section on mechanism). This, in the face of the associated increase in intestinal calcium absorption, may, therefore, lead to the development of hypercalcemia. In support of this contention is the observation that oral calcium loads which are well tolerated by normal subjects may produce severe hypercalcemia in hypothyroid patients.[31]

Hypoadrenocorticism (Addison Disease)

Glucocorticoids (GC) appear to play an important role in modulating the metabolism of parathyroid hormone[253,254] and its influence on calcium homeostasis.[254-257] Its absence leads to a loss of dampening influence on parathyroid hormone action and an increase in serum calcium concentration. Hypercalcemia has been documented in experimental adrenalectomy in animals,[255,258] in adrenocortical insufficiency in man[10,259-262] and in patients with the Cushing syndrome after therapeutic adrenalectomy.[263] Replacement doses of GC in these situations is always associated with dramatic resolution of the hypercalcemia. However, the effect of GC on plasma calcium concentration is not entirely explainable on the basis of its coupled action with PTH. For example, it lowers serum calcium concentration in parathyroidectomized rats.[256] In a variety of nonparathyroid dependent hypercalcemic conditions in which the endogenous parathyroid hormone secretion is presumably suppressed, GC is effective in lowering the serum calcium (refer to section on treatment). Moreover, acute hypocalcemia in rats following parathyroidectomy can be prevented by concomitant adrenalectomy,[256] and adrenalectomy in parathyroidectomized animals may lead to the development of overt hypercalcemia.[255] The role of GC in plasma calcium metabolism will be further discussed in the section on treatment.

Pheochromocytoma

The association between hypercalcemia and pheochromocytoma has been repeatedly documented. The best known clinical example is the multiple endocrine neoplasia type IIa or the Sipple syndrome which consists of medullary thyroid carcinoma, pheochromocytoma and parathyroid disease.[189,190] The coexistence of pheochromocytoma and hyperparathyroidism without medullary carcinoma has also been reported.[264] Hypercalcemia and hyperparathyroidism in these patients do not resolve with surgical removal of the pheochromocytoma.

There are, however, at least five case reports of pheochromocytoma associated with hypercalcemia (12 to 13 mg per dl) which resolved completely following surgical removal of the catecholamine-secreting tumor.[265-269] One postulate was that catecholamine excess may directly stimulate the parathyroid gland. In support of this thesis were the observations that acute infusions of β-adrenergic catecholamines in cows and in man result in increased PTH secretion, and the administration of propranolol, a β-adrenergic blocker, annuls the effect.[270,271] α-adrenergic catecholamines result in a lesser degree of stimulation. The difficulty with this thesis is that hypercalcemia is only infrequently seen in patients with pheochromocytoma. Parathyroid hormone was measured in two of the five reported patients. In one patient it was initially high in the presence of hypercalcemia. Following the removal of pheochromocytoma, the parathyroid hormone level normalized, as did the serum calcium concentration.[265] In the other patient, parathyroid hormone was not detectable either before or after the operation.[269]

Acromegaly

In a study of 78 untreated patients with acromegaly, about 16 percent were found to have hypercalcemia.[272] Sjöberg measured the rentention of oral ^{47}Ca in 12 patients with acromegaly and concluded that the intestinal calcium absorption in this population is increased. Interestingly, none of the patients studied was hypercalcemic.[273] Other biochemical features in acromegaly include hyperphosphatemia, hypophosphaturia and hypercalciuria.[272-274] Microradiographic analysis of skeletal biopsy specimens from acromegalic patients shows an increase in both bone forming and bone resorbing activities.[275] The increase in bone turnover activities may predispose these patients to the development of hypercalcemia upon immobilization, vide infra. The association between acromegaly and hyperparathyroidism in the syndrome of multiple endocrine adenomatosis has already been mentioned. The possibility that hypersomatotropism may directly stimulate parathyroid glands has been raised since Erdheim first reported hyperparathyroidism in an acromegalic patient.[276] Lancer and co-workers have shown parathyroid hyperplasia in rats given exogenous growth hormone.[277] However, in man Aloia and associates found increased serum parathyroid hormone levels in only one of the six acromegalic subjects studied.[274] The role of growth hormone in vitamin D metabolism has received much attention recently.[117] Hypophysectomy in rats leads to a reduction in the amount of tritiated 1α,25-dihydroxycholecalciferol (^3H-1,25$(OH)_2D_3$) in the intestinal mucosa and serum.[278] Administration of purified human growth hormone to hy-

pophysectomized rats restores to normal the depressed plasma levels of $1,25(OH)_2D_3$.[278a] However, growth hormone given to intact rats rather unexpectedly leads to a decrease in conversion of tritiated 25 hydroxycholecalciferol (^3H-$25(OH)_2D_3$) to ^3H-$1,25(OH)_2D_3$.[278] Other workers showed there to be an increase in the conversion of $25(OH)D_3$ to its 24-hydroxylated metabolite in hypophysectomized rats fed a normal diet.[278b]

Pharmacological Agents

Vitamin D and Its Metabolites

In the past, cases of overdosage of vitamin D_2 (ergocalciferol), vitamin D_3 (cholecalciferol), dihydrotachysterol (Hytakerol®, AT10 in Europe) were usually the result of using these compounds in the empirical treatment of a variety of disorders including rheumatoid arthritis, hay fever, asthma, sarcoidosis and tuberculosis.[279-282] Nowadays, the use of vitamin D and related compounds is mainly restricted to the treatment of hypoparathyroidism, rickets (D-deficient, D-dependent and D-resistant) and uremic osteodystrophy. Vitamin D-overdose is therefore most commonly found in these patients, although, occasionally, self-induced intoxication may be the cause.[283,284]

The hypercalcemia of vitamin D intoxication is mainly the result of a combination of increased bone resorption and intestinal absorption of calcium. Clinical manifestations include mental symptoms; normocytic anemia; weakness; fatigue; weight loss; nephrocalcinosis and nephrolithiasis; impaired renal conservation of water, sodium and potassium, and a decreased ability to excrete an acid load secondary to a decreased renal tubular production of ammonia.[279,280,285,286]

In vitro studies suggest that pharmacologic doses of vitamin D_3 are taken up passively by the small gut.[287] Under intoxication conditions, the plasma level of 1,25-dihydroxycholecalciferol ($1,25(OH)_2D_3$) may be normal although the conversion of vitamin D to $25(OH)D_3$ is considerably increased.[288] The administration of large doses of vitamin D_2 to rats is associated with the development of calcinosis of the coronary artery, the myocardium, the media of the aorta, lungs, pleura and gastrointestinal tract. In the kidney, focal calcification of the juxtaglomerular apparatus and focal necrosis of the proximal tubular epithelium are observed while the glomerulus is left unscathed. Finally, in a study in pregnant animals impaired fetal growth and increased fetal mortality and morbidity were noted.[289] A study in pregnant rabbits showed transplacental crossing of vitamin D and the development of supravalvular aortic stenosis in the offspring.[290] The toxicity of the hormonal forms of vitamin D has recently been studied by Makita and associates.[291] Morphological lesions observed included necrosis of the intima of the heart, gut and muscle arterioles.

The plasma biologic half-life of vitamin D in humans, following administration of large doses of this agent, has been estimated to be about three months.[292,293] There are great individual variations in the duration and dosage of vitamin D administration before the appearance of toxicity.[282] The basis for this difference remains to be fully elucidated and may include individual variations in factors such as fat storage, binding proteins and activation of vitamin D. Connors, Sheikholislam and Irias reported the development of hypercalcemia in a patient with idiopathic hypoparathyroidism after voluntary weight reduction. For the previous ten months, while maintained on the same dose of vitamin D, he was persistently hypocalcemic. The authors postulated that the toxicity was due to release of stored vitamin D into the circulation.[294] The time required for return of calcium to normal levels after intoxication averaged two to five months but may take as long as 22 months.[295] More recently, Kanis and Russell[205] reported calculated half-times for reversal of hypercalcemia and hypercalciuria after cessation of $1\alpha,25$-dihydroxycholecalciferol ($1\alpha,25(OH)_2D_3$), 1α-hydroxycholecalciferol ($1\alpha(OH)D_3$) and calciferol as 1.5 ± 0.2, 3.5 ± 0.4, 29.5 ± 9.1 days (mean $\pm$ SE of mean). The equivalent half-time for dihydrotachysterol was 44 days. Others claim that recovery from the toxicity of dihydrotachysterol is more rapid than that of calciferol.[285]

Infants appear particularly susceptible to vitamin D toxicity.[296,297] The dramatic increase in the incidence of infantile hypercalcemia during World War II in England was attributed to the oversupplementation of vitamin D in the diet. More recently, Linden[298] reviewed the subject and confirmed the observation that a modest excess of vitamin D may lead to disseminated arteriosclerosis, supravalvular aortic stenosis, renal acidosis and chronic hypercalcemia of infancy. Others[299] have found that skin fibroblasts from children with the supravalvular aortic stenosis-infantile hypercalcemia syndrome show increased sensitivity to vitamin D_2 when compared to specimens

obtained from normal children. They interpreted their data as suggestive of a genetically predetermined hypersensitivity to vitamin D in this syndrome. More recently, some authors have questioned the hitherto assumed association between infantile hypercalcemia and supravalvular aortic stenosis.[300,301] Daiger and associates[302] distinguished Williams syndrome (a congenital disorder with mental and mild growth deficiency, elfin facies, supravalvular aortic stenosis and, occasionally, elevated levels of serum calcium) from familial idiopathic hypercalcemia. In both conditions vitamin-D-binding protein was normal both quantitatively and qualitatively.

Of interest is the study relating coronary heart disease and elevated blood cholesterol to high vitamin D consumption in a group of farmers.[303] It has also been shown that vitamin D increases the uptake and incorporation of radioactive phosphorus into phospholipids.[304] There was also an increase in hepatic cholesterol, total fat and fatty acid content. Curcic and Curcic studied a large number of children with rickets treated with varying doses of vitamin D. After one month, a slight increase in blood pressure and serum cholesterol was seen in most of the subjects.[305]

Vitamin A

The interesting syndrome of headache, vertigo and diarrhea following ingestion of bear liver was noted by arctic explorers in 1857.[305] Clinically, vitamin A intoxication is an infrequent but important cause of hypercalcemia. It is most often the result of ill-advised, inadvertent or surreptitious ingestion of large amounts of vitamin A containing preparations.[307-309] With the recent increase in publicity attesting to the supposed value of vitamin A as a nutritional supplement and as a treatment modality for acne vulgaris and other skin conditions, the incidence of vitamin A-induced hypercalcemia may be expected to rise. Childhood blindness is another condition in which massive doses of vitamin A have been used with no proven benefit but clear toxicity.[310]

There is both experimental and clinical evidence suggesting that hypervitaminosis A can cause increased bone resorption and periosteal calcification.[311-313] However, the precise pathogenesis of vitamin A toxicity is still obscure.[309] The complex interrelationship between vitamin A and cell membrane phenomena and cell functions has been studied by a number of investigators.[314-318] Altered choroid plexus membrane function may be related to the so far unresolved question of the mechanism of increased cerebrospinal fluid pressure in vitamin A toxicity.[319-321]

Preliminary observations suggest that renal dysfunction may lead to a state of intolerance to vitamin A. Children with lipoid nephrosis have increased levels of circulating vitamin A and are more sensitive to ordinary doses of the vitamin.[322] A high serum vitamin A level has also been blamed for the syndrome of anorexia, skin dryness, nausea and headache in patients with advanced renal failure.[323]

Reported experimental teratogenic effects of vitamin A include cleft palate, fused ribs, spina bifida, meningocele, hydronephrosis, and heart and genitourinary abnormalities.[309] A case of congenital salt-losing nephritis has been attributed to hypervitaminosis A.[324] Although increased serum level of vitamin A is seen in women taking oral contraceptives,[325,326] there is no clear evidence suggesting increased fetal abnormalities in this population.[327] Chronic hypervitaminosis A can also lead to cirrhotic-like liver damage with portal hypertension and ascites.[328]

Milk-Alkali Syndrome

The term milk-alkali syndrome arose from a report by Burnett and co-workers[329] in 1949: "The syndrome is characterized by a history of prolonged and excessive intake of milk and absorbable alkali; hypercalcemia without hypercalciuria or hypophosphatemia; normal alkaline phoshatase levels; marked renal insufficiency with azotemia; mild alkalosis; calcinosis manifested especially by ocular lesion resembling band keratitis; and an improvement on an intake low in milk and absorbable alkali." All of Burnett's six patients had ingested large amounts of milk and absorbable alkali for a prolonged period—3 to 30 years. At the time when they were seen for hypercalcemia, blood urea nitrogen (BUN) ranged from 58 to 131 mg per dl. The absence of both hypercalciuria and hypophosphatemia were probably consequences of renal failure and would not necessarily constitute evidence against the diagnosis of primary hyperparathyroidism as implied by the authors. The improvement following reduction in milk and alkali consumption consisted mainly of symptomatic relief which was not necessarily lasting. In two patients, hypercalcemia was replaced by hypocalcemia associated with worsening of renal function: BUN 58 to 150 and 78 to 160 mg per dl, respectively. In the remaining four

patients, hypercalcemia improved although in only one patient was normocalcemia achieved (9.1 mg per dl), associated with an improvement in BUN from 131 to 71 mg per dl. Four of the six patients died 27 to 78 months after first seen with hypercalcemia—three probably from renal failure with BUN over 125 mg per dl, and the remaining one "failed progressively" and died. The other two patients were alive at 5 and 15 months but with moderately severe renal failure (BUN 71 and 75 mg per dl, respectively).

The chemical constellation of hypercalcemia, azotemia and variable elevation of serum phosphorus and carbon dioxide content may also develop acutely within days after therapy with a large amount of reputedly nonabsorbable alkali such as calcium carbonate. The clinical symptomatology may be dramatic and includes nausea, vomiting, anorexia, distaste for milk, weakness, lethargy, headache, dizziness and mental changes. This symptom complex was first described by Hardt and Rivers in 1923[330] in 16 patients treated with milk and Sippy powder (calcium carbonate, sodium bicarbonate, magnesium oxide and bismuth subcarbonate). Wenger and associates,[331] as well as McMillan and Freeman,[332] reported similar reactions in patients treated with milk and calcium carbonate. The acute syndrome differs from the chronic form described by Burnett in the absence of soft tissue calcification and the rapid and complete relief of symptoms and reversal of biochemical and renal functional changes upon withdrawal of milk and alkali.

In addition, an intermediate form of milk-alkali syndrome has also been described. These patients usually have been taking milk and alkali intermittently for years. The condition resembles the acute form in symptomatology and in the absence of soft tissue calcification. Resolution of symptoms and reversal of chemical and renal abnormalities tend to be less rapid than in the acute form, but more complete than in the chronic form.[333,334]

The mechanism of hypercalcemia is not completely understood but is traditionally attributed to excessive calcium absorption. Under normal circumstances, the rate of intestinal calcium absorption is physiologically adjusted to the amount of calcium ingested so that the total quantity absorbed remains relatively constant.[335] The reason for the apparent breakdown in this adaptive mechanism in the milk-alkali syndrome is not clear.

The mechanism for the development of alkalosis is also not clearly defined. Theoretically, alkalosis is generated and sustained by the combination of an increased alkali load associated with a decreased ability of the kidney to eliminate the load.[336] The alkali load in milk-alkali syndrome would consist of excessive ingestion augmented by endogenous generation through recurrent vomiting. Impaired renal ability to excrete bicarbonate may result from (1) hypercalcemia which may accelerate bicarbonate reabsorption by a direct effect on the renal tubule,[337] (2) hypokalemia which may accompany milk-alkali syndrome and (3) hypovolemia which may result from intractable vomiting. In addition, both hypoparathyroidism, secondary to hypercalcemia, and hyperphosphatemia (through its possible effect on renal intracellular pH) have been postulated to play a contributory role in enhancing renal bicarbonate reclamation.[338]

Thiazide Diuretics

Sustained thiazide diuretic administration predictably reduces urinary calcium excretion. Postulated mechanisms of action include (1) extracellular volume depletion,[339,340] (2) direct stimulation of the parathyroid glands,[341] (3) potentiation of the renal calcium conserving action of parathyroid hormone[340,342] and (4) direct drug action on the kidney.[343]

An increase in serum calcium concentration following the use of thiazide diuretics has been reported in normal subjects,[344] in patients on hemodialysis[345] and in patients with bone diseases characterized by high turnover rates such as in primary hyperparathyroidism,[346,347] vitamin D treated hypoparathyroidism[348] or juvenile osteoporosis.[346]

Popovtzer and associates noted an acute but transient increase in serum calcium concentration two hours after the beginning of intravenous infusion of chlorothiazide (3.33 mg per kg of body weight per hour) in normoparathyroid subjects. This hypercalcemic effect was not seen in hypoparathyroid patients but was sustained in hyperparathyroid patients. They suggested that the acute administration of chlorothiazide may enhance parathyroid hormone action on the bone. The transient nature of the thiazide-induced hypercalcemia in normoparathyroid patients is attributed to the suppression of parathyroid hormone secretion as a result of the initial rise in serum calcium concentration. When exogenous

parathyroid hormone was given together with chlorothiazide in normal subjects, the induced hypercalcemia became persistent. These authors therefore concluded that the acute hypercalcemic action of chlorothiazide is parathyroid hormone dependent.[349] Brickman and associates[340] administered hydrochlorothiazide orally, 100 mg twice a day for four days, and also noted an increase in serum calcium concentration in normal subjects, hyperparathyroid patients and hypoparathyroid patients treated with vitamin D. The hypercalcemia in normal subjects was entirely accounted for by changes in serum calcium concentration secondary to hemoconcentration. On the other hand, in patients with hyperparathyroidism and in vitamin D-treated hypoparathyroid patients, there was a clear increase in serum calcium concentration independent of changes in plasma protein concentration. These authors postulated that thiazide may increase the release of calcium from bone into ECF in states characterized by augmented bone resorption. Both studies, therefore, suggest that in normal subjects the distortion in serum calcium concentration by thiazide administration may be corrected by normal homeostatic mechanisms (feedback suppression of parathyroid hormone secretion or reexpansion of ECF volume). Sustained hypercalcemia is induced only in patients with persistently abnormal parathyroid hormone secretion or in patients with increased bone resorption activities, with or without high circulating parathyroid hormone levels.

The study of Stote and associates,[350] however, is at variance with the above conclusions. In this study, normal subjects were given 50 mg of hydrochlorothiazide twice a day for 25 days. Total serum calcium concentration increased significantly after one day and ionized calcium concentration increased significantly after 17 days of hydrochlorothiazide administration. Both remained significantly increased two weeks after cessation of therapy. No clearly definable influence was noted on either protein-binding of calcium or circulating immunoreactive parathyroid hormone (iPTH). Moreover, the negative correlation between ionized calcium and iPTH appeared normal. The mechanism of the hypercalcemia was not elucidated. It is important to point out that a significant increase in ionized calcium concentration did not develop until the 17th day of thiazide administration. Popovtzer and associates[349] condueted their study over eight hours and Brickman and associates[340] over four days. Complete understanding of the mechanism of thiazide-induced hypercalcemia therefore awaits further investigation.

Calcium

The role of calcium administration in the generation of hypercalcemia in hypothyroidism, hypoparathyroidism, chronic renal failure and milk-alkali syndrome has already been discussed. Hypercalcemia has also been described in parenteral hyperalimentation when excessive calcium is administered.[351]

Lithium

Several cases of hypercalcemia following lithium-carbonate ingestion have been described.[352] Hypercalcemia disappeared after discontinuation of lithium administration and reappeared after lithium was reinstituted. In patients in whom surgical exploration was done, parathyroid adenoma was discovered and removed in all. The possibility of lithium uncovering normocalcemic hyperparathyroidism, in a manner analogous to thiazide-induced hypercalcemia, has been raised. Christiansen and associates[353] studied 96 lithium-treated manic depressive patients and found a significant increase in serum concentrations of PTH, calcium, and magnesium when compared with normal controls. In 14 patients serum PTH levels were clearly above the normal range (mean + 2 SD). The basic mechanism and interrelationship clearly deserve further studies.

Possible Increased Sensitivity to Vitamin D

Chronic Granulomatous Disease and Sarcoidosis

Hypercalcemia develops in 10 percent to 30 percent of patients with sarcoidosis.[354] Hypercalciuria, in the absence of hypercalcemia, is about three times as common.[355] Reiner and associates,[356] however, found only one case of hypercalcemia in 66 sarcoid patients seen at a chest clinic over ten years, although calcium metabolic abnormalities such as intestinal hyperabsorption and increased bone turnover rate were present in about 50 percent of the patients in whom such disturbances were specifically looked for. The variation in the incidence of hypercalcemia in this disease may be the result of a large number of factors including dietary mineral and vitamin content and the extent of sun exposure in the population studied. Pronounced hypercalcemia, metastatic calcification and renal insufficiency have been documented in a number of patients.[357-359]

The metabolic characteristics of hypercalcemia, hypercalciuria and a decrease in fecal calcium in sarcoidosis resemble those found in hypervitaminosis D. However, plasma levels of total vitamin D activity (antirachitic activity) have been found to be normal or low.[360-363] Plasma levels of $25(OH)D_3$ and the conversion of $25(OH)D_3$ to $1,25(OH)_2D_3$ have both been reported to be normal.[364] In the absence of an endogenous excess of vitamin D or its metabolites, the concept of a state of hypersensitivity to vitamin D was developed. Several observations have been used in support of such a concept. Hypercalcemia and toxicity sometimes develop in patients with sarcoidosis given small doses of vitamin D that are well tolerated by the general population.[365,366] Exacerbation and increased incidence of hypercalcemia have been reported in patients with sarcoidosis following exposure to ultraviolet light or during the summer months with greater exposure to sunlight.[367,368] Vitamin D depletion, on the other hand, ameliorates the disturbance in calcium metabolism.[369] There is also generally an excellent response of sarcoid hypercalcemia to glucocorticoid therapy[365] and failure to respond to such therapy has been suggested as evidence for coexistent hyperparathyroidism.[370-373]

Parathyroid hormone excess is unlikely to play a major role in the calcium metabolic disturbance of sarcoidosis. The phosphate excretion index is normal or low[356,374]* and the urinary calcium excretion is high even in the absence of hypercalcemia[356]—findings suggestive of reduced biological effect of parathyroid hormone. In patients with established hypoparathyroidism, the development of sarcoidosis leads to the amelioration of hypocalcemia and may even result in the appearance of frank hypercalcemia.[376,377] Finally, Cushard and associates[378] reported undetectably low parathyroid hormone levels in sarcoid patients with or without hypercalcemia. Interestingly, PTH was also suppressed in normocalcemic patients and that in five of seven patients treated with steroids, the PTH levels rose to the normal range. On rare occasions, however, the expected suppression of PTH is not found. In a recent case of hypercalcemia with normal to elevated immunoreactive parathyroid hormone, the diagnosis of sarcoidosis was not made until the mediastinum was split in search of the nonexistent fifth parathyroid gland.[379] The state of the art is further complicated by the occasional coexistence of hyperparathyroidism and sarcoidosis.[158,370,380,381]

Although several balance studies have shown a net increase in intestinal calcium retention,[363,365,382] the development of hypercalcemia is probably not a single consequence of calcium hyperabsorption. The observation that hypercalcemia may develop even in the face of very low calcium intake[383] lends credence to such an assumption. The lack of a cause and effect relationship between calcium hyperabsorption and hypercalcemia in patients with sarcoidosis is also clear from the findings of a study by Reiner and associates.[356] These authors showed an increase in calcium absorption in six of 13 unselected, untreated patients with sarcoidosis. In all 13 patients serum calcium concentrations were normal. On the other hand, Hornum and Transböl[375] found hypercalcemia in the face of normal intestinal calcium absorption.

The amelioration of sarcoid hypercalcemia by glucocorticoids is therefore not completely, if at all, attributable to the correction of intestinal calcium hyperabsorption. Since glucocorticoids also have important effects on calcium metabolism outside the intestine (see section on treatment), extraintestinal mechanisms in the generation of hypercalcemia in sarcoidosis remain open possibilities. It is recognized that urinary calcium excretion in this condition frequently exceeds that which could be expected from intestinal absorption alone and therefore further implicates the coexistence of abnormalities of calcium metabolism in addition to intestinal hyperabsorption.[366,369,382] Although direct skeletal erosion by sarcoid tissue is considered an unlikely and unimportant cause for sarcoid hypercalcemia,[384-387] the possibility of endogenous generation of a nonparathyroid, nonvitamin D related bone resorbing hypercalcemic agent in patients with sarcoidosis remains to be explored. Indeed, a number of studies have shown evidence for increased bone turnover or bone resorption (or both) in patients with sarcoidosis.[356,366,369,375] However, systematic investigation of quantitative aspects of cellular and mineral metabolism of bone in sarcoid patients has so far received scant attention. The possible role of mobilization of extraosseous metastatic calcifications in sustaining sarcoid hypercalcemia during certain phases of the disease has also been suggested.[375]

Hypercalcemia may also complicate other systemic granulomatous diseases such as berylliо-

*Others,[375] however, have found low levels of tubular reabsorption of phosphate.

sis,[388] tuberculosis,[389] histoplasmosis[390] and coccidioidomycosis.[391]

Idiopathic Infantile Hypercalcemia

This entity has already been discussed in the section on vitamin D toxicity.

Miscellaneous Causes of Hypercalcemia

Physiological Hypercalcemia

Bergman and Isaksson[392] studied plasma calcium fractions in 202 normal children and 93 men. Their results are reproduced in Figures 13 and 14. The mean values for both total (11.6 mg per dl) and ultrafiltrable calcium (7.7 mg per dl) at birth were significantly higher than in all other age groups. These values then declined to a minimum of 9.0 and 5.7 mg per dl, respectively, by 24 to 48 hours. An increase was then seen during the first week of life so that the mean value for total and ultrafiltrable calcium for the 9 to 90 day age group was 10.6 and 6.7 mg per dl. Both total and ultrafiltrable calcium then decreased continuously with age to the adult level of 9.7 and 5.6 mg per dl. The changes in total plasma calcium levels are accountable by changes in ultrafiltrable calcium. In 24 to 48 hours of life and five to seven days of life, protein bound calcium was significantly lower as well. The mechanism for this hypercalcemia is not well understood, but is probably related to the state of pronounced positive calcium balance and skeletal mineralization associated with rapid growth. Parenthetically, in the adult population, among subjects under 50, the mean serum calcium level is significantly higher in men. The calcium concentration in men decreases with increasing age so that the mean values for men and women over 50 are equal.[40]

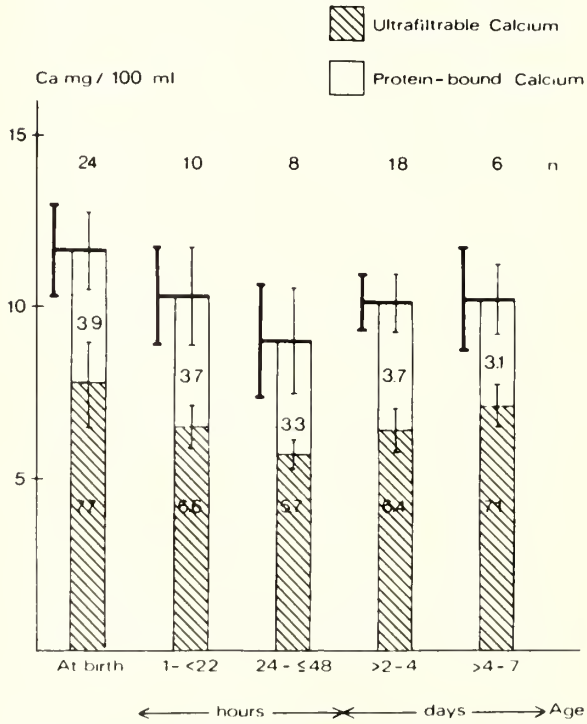

Figure 13.—Distribution of plasma calcium during the first week of life; 66 normal cases. Mean values and standard deviations for total calcium (thick bars), ultrafiltrable calcium and protein-bound calcium are given. All values corrected to pH 7.4. [Reprinted from Bergman and Isaksson[392] with permission.]

Immobilization Hypercalcemia

Immobilization or disuse of part or all of the body can lead to the development of osteoporosis in the part of the skeleton immobilized. Mechanical restriction with a cast, weightlessness, nerve section and other forms of paralysis are some of the causes leading to disuse osteoporosis.[393-398] Loss of bone minerals is associated with hypercalciuria and, sometimes, renal calculi formation. The development of hypercalcemia is not frequent and usually occurs only in patients with states of rapid bone turnover. Most cases of immobilization hypercalcemia occurred in previously normal children (usually boys) between the ages of 9 and 14. Women and young adults, however, are not immune.[396,398] In adults, immobilization hypercalcemia almost always occurs in patients with preexisting bone disease such as Paget disease, neoplasia and primary hyperparathyroidism[399,400] Hypercalcemia has also been reported in patients

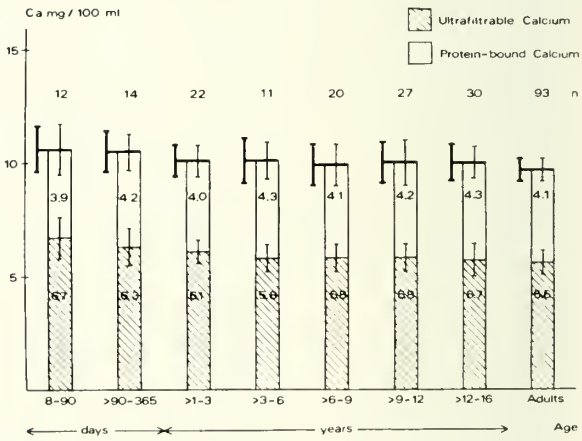

Figure 14.—Distribution of plasma calcium after the first week of life up to adults; 229 normal cases. Mean values and standard deviations for total calcium (thick bars), ultrafiltrable calcium and protein-bound calcium are given. All values are corrected to pH 7.4. [Reprinted from Bergman and Isaksson[392] with permission.]

with renal osteodystrophy immobilized because of pathological fractures.[210] The severity of immobilization hypercalcemia varies and may become life-threatening.[393,395]

The development of acute osteoporosis from disuse suggests that mechanical forces have important influences on bone formation and resorption. It has been postulated that this effect may be brought about by the induction of electric fields within bones which modify the behavior of bone cells.[401] Both increased bone resorption and decreased bone formation have been described in this condition.[402-406] Parathyroidectomy results in pronounced retardation of the development of disuse osteoporosis, suggesting an increased sensitivity of the immobilized skeleton to the calcemic action of parathyroid hormone and perhaps other calcium homeostatic agents.[404]

The clinical differentiation of immobilization hypercalcemia from primary hyperparathyroidism may sometimes be difficult.[393,396] This problem is not simplified by the advent of direct parathyroid hormone measurement. Different groups of investigators have reported low,[407] normal[394,397] and elevated[395,408] levels of PTH in hypercalcemia associated with immobilization.

Other Hypercalcemic Conditions in Children

Disturbances in calcium metabolism, including hypercalcemia, in infants and children have recently been reviewed by Root and Harrison.[409] A rather unusual cause of hypercalcemia in this population is the entity termed subcutaneous fat necrosis.

Hypercalcemia in Acute and Chronic Renal Failure

Causes of hypercalcemia associated with acute and chronic renal failure have been discussed under the section on hypercalcemic secondary hyperparathyroidism.

Phosphorus Depletion in Uremic Patients

Hypercalcemia has been described in a few isolated cases of phosphorus depletion in uremic patients.[208,209] In general, hypercalcemia is not a feature of phosphorus depletion in adult dogs[410] and man.[411,412]

Finally, hypophosphatasia[413] and generalized periostitis[414] are extremely rare causes of hypercalcemia.

CLINICAL MANIFESTATIONS AND DIAGNOSTIC CONSIDERATIONS

The clinical manifestations of a given degree of hypercalcemia vary from person to person. Some patients are greatly distressed by only slight elevation in serum calcium concentration whereas others with levels of 15 mg per dl or higher may present with very little complaint.[415] In general, the severity of clinical manifestation is proportional to the rate of development and the degree of hypercalcemia, modified by factors such as age, associated electrolyte-metabolic abnormalities and underlying primary disorders. Figure 15 catalogues some of the features known to be associated with clinical hypercalcemic states. Only the less well-known features or features described in specific hypercalcemic syndromes are referenced in the figure. For additional manifestations and associated conditions in different syndromes of hypercalcemia, please refer to relevant sections in the discussion on causes of hypercalcemia.

Although the list of causes of hypercalcemia is impressively long (Table 2), and a variety of mathematical and computer approaches[416,417] have been suggested as aids in the search for correct causes, we have, in general, encountered little difficulty in arriving at the correct diagnosis without resorting to additional mechanical devices. Awareness of the clinical correlates and the natural history of the various hypercalcemic syndromes, coupled with skillfully elicited history and physical examinations, remains the cornerstone of the diagnostic workup for hypercalcemia.

Serum total calcium concentration should always be interpreted after correction for binding to albumin. Single elevation in serum calcium concentration should always be confirmed by repeated measurements. In a patient in whom a hypercalcemic condition is seriously suspected on clinical grounds, the findings of "normocalcemia" should be pursued further with repeated measurements of ionized calcium concentrations.[19-22,418,419]

Most laboratory evaluations of hypercalcemia are directed toward the differentiation of causes attributed to excessive parathyroid hormone production from causes that are independent of PTH. Traditionally, this has been accomplished by measuring a number of indices reflecting the action of PTH on various target organs, particularly the kidney (Table 3).

In general, severe hypercalcemia (greater than 14 mg per dl) suggests nonparathyroid causes,

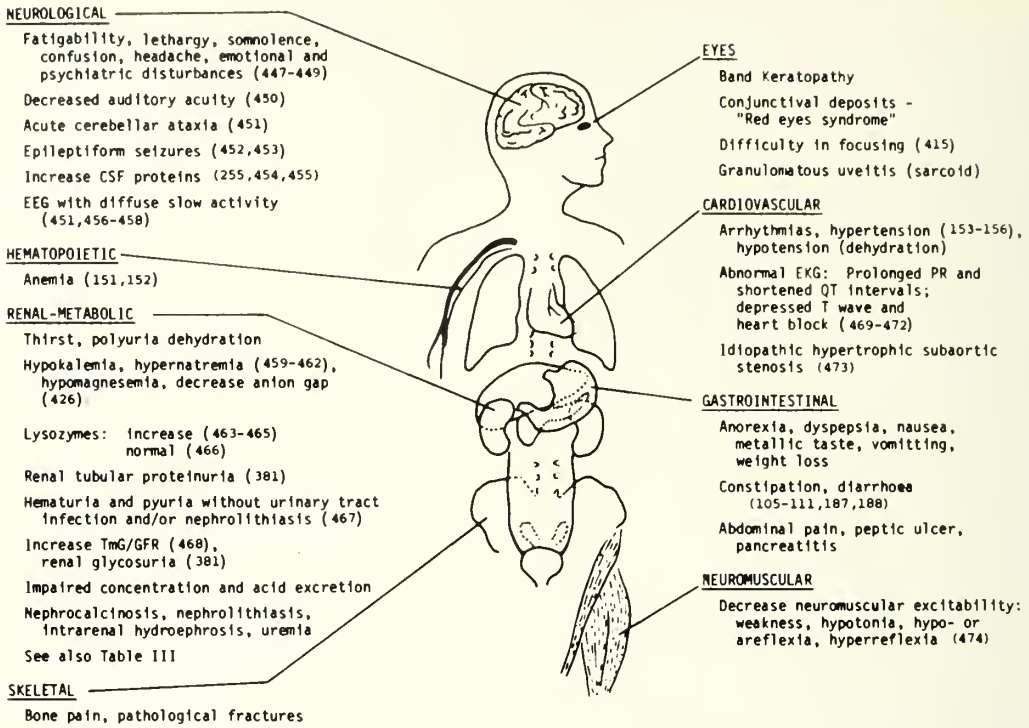

Figure 15.—Clinical features associated with hypercalcemia.

TABLE 3.—*Laboratory Differential Diagnostic Indices Between PTH-Dependent and Non-PTH-Dependent Causes of Hypercalcemia*

Indices	*PTH-Dependent*	*Non-PTH-Dependent*
Serum calcium	<14 mg/dl	>14 mg/dl
Azotemia	Usually absent	Usually present
Serum phosphorus	↓	N—↑
Serum bicarbonate	N—↓	N—↑
Serum chloride (mEq/liter) / Serum phosphorus (mg/dl)	>32	<32
Tubular reabsorption of calcium	↑	↓
Tubular reabsorption of phosphate	↓	↑
Urinary cAMP	↑	↓
Steroid suppression test	Serum calcium no change	Serum calcium ↓

↑ = increase
↓ = decrease
N = normal
PTH = parathyroid hormone
cAMP = cyclic adenosine monophasphate

usually malignant conditions. The hypercalcemia of parathyroid overactivity is, as a rule, milder, except in cases of carcinoma and acute hyperparathyroid crisis.[134,139-141] Well marked renal insufficiency is uncommon in patients with primary hyperparathyroid disease except in cases of carcinoma, or in patients with severe osteitis fibrosa. On the other hand, some degree of renal failure is the usual finding in patients with other causes of hypercalcemia such as malignancies, sarcoidosis and milk-alkali syndrome.[416,420] The known phosphaturic and bicarbonaturic actions of PTH are most likely the basis of low serum phosphorus and bicarbonate concentrations and a high serum chloride (mEq per L) : serum phosphorus (mg per dl) ratio[412,422]* observed in a variable number of patients with hyperparathyroidism. In nonparathyroid hypercalcemias, the anticipated suppression of endogenous parathyroid hormone secretion would be expected to result in a reversal of changes in these indices. The metabolic alkalosis in these latter conditions is probably further accentuated by the release of alkalis from the skeleton, secondary to bone destruction and increase in bone turnover rate.[425] The interpretation of acid-base indices in hypercalcemic patients must always include the considerations of modifying factors such as nausea and vomiting, renal insufficiency and the influence of hypercalcemia on anion-gap.[426]

Renal excretion of calcium, phosphorus and cyclic adenosine monophosphate (cAMP) form

* The discriminatory value of low serum phosphorus[420] and low serum bicarbonate[423] concentrations and the chloride/phosphorus ratio[424] have all been questioned by various authors.

another group of studies aimed at differentiating states of excessive effective parathyroid hormone from states of absent PTH in the circulation.

Transböl and associates found that the measurement of tubular reabsorption of calcium (TRCa percent) under standardized conditions was useful in the differential diagnosis of hypercalcemic syndromes.[427] They found TRCa percent was increased in 49 of 56 patients (88 percent) with hyperparathyroidism and in a patient with pseudohyperparathyroidism, but was reduced in 17 of 19 patients (89 percent) with non-PTH dependent hypercalcemias.

Tubular reabsorption of phosphate (TRP) is a well-used index, traditionally believed to reflect the activity of the parathyroid glands. However, since PTH is only one of the several factors known to influence renal handling of phosphate,[428] the use of TRP as an acceptable indicator of PTH activity would require rigid and cumbersome control of conditions under which it is measured. Llach and associates measured TRP after five days of oral phosphate loading in normal subjects, patients with hyperparathyroidism, subjects with idiopathic hypercalciuria and patients with hypercalcemia due to malignant disease.[429] A great deal of overlap was observed between the basal values of TRP in normal subjects and in patients with these calcium disorders before phosphate loading. After loading, TRP fell substantially in all subjects except in those with hypercalcemia due to malignant disease, thereby separating the latter patients from those with hyperparathyroidism. In hyperparathyroid patients after phosphate loading, the TRP fell to lower levels than those observed in normal subjects, with no overlap between individual values. The authors therefore proposed the five-day phosphate loading test as a useful maneuver in separating normal subjects from patients with hyperparathyroidism.

Data from a number of laboratories suggest a direct correlation between circulating PTH activity and renal excretion of cAMP.[430,431] However, like phosphate excretion, the reliability of total urinary cAMP as an index of PTH activity is considerably impaired by the finding that a host of other conditions and factors may modulate the urinary content of cAMP.[432] However, the diagnostic accuracy of urinary cAMP may be greatly enhanced by the derivation or actual determination of nephrogenous cAMP.[433]

The role of glucocorticoid administration in the differential diagnosis of PTH from non-PTH dependent forms of hypercalcemia is discussed in the section on treatment.

The recent development and steady improvement in the knowledge and measurement of various metabolites of PTH[434,435] have progressively rendered the various indirect tests of PTH activity less popular and obsolete. However, a number of basic inconsistencies remain to be resolved in the measurement of parathyroid hormone by the radioimmunoassay technique.[72] Direct measurement of PTH may, on occasions, be the only method in distinguishing primary hyperparathyroidism from ectopic hyperparathyroidism of malignancy. In some patients with the latter condition, a larger PTH fragment may be the predominant circulating immunoreactive form of PTH, whereas radioimmunologically, a similar fragment is found in much smaller amounts in the serum of patients with primary hyperparathyroidism.[71]

The development of various techniques for localizing pathologic parathyroid glands before surgical operation continues to interest a number of investigators. These include thermography,[436] ultrasound, radioisotope scans,[437,438] angiography[439,440] and measurement of PTH in blood obtained from veins draining the parathyroids.[439,441] In general, these methods reliably detect only those glands which are large enough to be easily found by an experienced surgeon without prior knowledge of their location. The techniques of venous sampling and angiography, considered to be of greater sensitivity by some workers, are also more invasive and costly. Selective arteriography and venous sampling, however, may earn a justifiable role in locating the culprit gland when a careful first operation has failed.[439] It is important to note that PTH gradient from major neck veins has been documented not only in hypercalcemic patients with PHPT[442] but also in patients without abnormalities of calcium metabolism[443] and in patients with hypercalcemia of nonparathyroid origin.[85] This underscores the importance of sampling from small thyroidal veins if venous catheterization is used to localize hyperfunctioning parathyroid glands.[444,445]

Radiological examination of the skeleton and soft tissue is an important component in the diagnosis and assessment of a patient with hypercalcemia. Cystic lesions and osteopenia generally suggest the diagnosis of hyperparathyroidism. Infrequently, primary hyperparathyroidism is associated with osteosclerosis.[446] However, when cystic lesions are associated with "punched out"

phalangeal lesions and serum phosphorus concentration in the high normal range, the diagnosis of sarcoidosis should be seriously suspected. Blastic or lytic lesions would suggest malignancy as the underlying cause. Sometimes skeletal lesions which are not detectable by x-ray studies may be visualized by bone scan.

The various hypercalcemic syndromes and their diagnostic characteristics and associations have already been discussed under the various headings in the section on causes of hypercalcemia.

THE MANAGEMENT OF HYPERCALCEMIC DISORDERS

The management of hypercalcemia will be discussed under three headings (Table 4). All patients with established diagnosis of hypercalcemia should receive the benefit of general supportive measures which aim to prevent a further increase in serum calcium concentration and the development of complications related to hypercalcemia. The need and speed with which to institute measures for lowering serum calcium concentration would depend on the severity and the duration of hypercalcemia. In an ambulatory, asymptomatic patient with mild hypercalcemia, the management (Table 4) may involve direct progression from general measures to specific measures of eradicating the primary cause without the need for the intervention with the more heroic, and sometimes hazardous, means of lowering serum calcium concentration.

General Measures

Dehydration and electrolyte depletions constitute one of the most common modes of presentation. This is hardly surprising since hypercalcemia is associated with anorexia, nausea, vomiting and polyuria. Therefore, the first and the fundamental step in the management of any hypercalcemic patient is the prompt restoration of euvolemia using normal saline. The most frequent electrolyte disturbance is hypokalemia,[460] less often hypomagnesemia, both of which, when present, should be appropriately corrected.

Administration of medications known to elevate serum calcium concentrations should obviously be discontinued. This will include vitamins A and D, thiazide diuretics and sex steroids in patients with breast cancer. The possible role of lithium in causing hypercalcemia has already been discussed. The dosage of medications whose action is influenced by serum calcium concentration should be appropriately adjusted. One such medication in common use is digitalis which acts synergistically with calcium on the myocardium and the conducting system. If the situation is further complicated by hypokalemia, critical digitalis toxicity may develop. Close clinical and electrocardiographic monitorings on such patients are clearly essential.

Protracted immobilization may be unavoidable in certain very sick patients. Under such circumstances, normal turning and some specially tailored physical therapy in bed may be all the mobilization one can institute. In other patients, close coordination with a dedicated physical therapist, judicious use of analgesics and planned orthopedic

TABLE 4.—*Management of Hypercalcemia*

General Measures
- Correct hypovolemia
- Correct associated electrolyte abnormalities
- Appropriate adjustment of medications
- Encourage mobilization

Measures for Lowering Serum Calcium Concentration
- Enhance calcium loss through urinary excretion or dialysis
  - Intravenous saline loading, with or without furosemide or ethacrinic acid
  - Disodium ethylenediaminetetraacetate
  - Intravenous sodium sulfate and sodium citrate
  - Hemodialyses and peritoneal dialysis
- Increase net movement of calcium into bone
  - Decrease movement of calcium from bone into extracellular fluid
    - Calcitonin
    - Mithramycin
    - Corticosteroids
    - Others: prostaglandin inhibitors, propranolol, estrogens
  - Increase movement of calcium from extracellular fluid into bone
  - Parenteral and/or oral inorganic phosphate
- Decrease intestinal calcium absorption
  - Corticosteroids
  - Reduce calcium intake
  - Decrease availability of dietary calcium
    - Oxalate-containing foods
    - Sodium phytate
    - Cellulose phosphate

Specific Measures for Correcting Primary Cause
- Parathyroidectomy
- Tumor ablation
  - Surgical (including endocrine ablation in breast cancer)
  - Nonsurgical: Corticosteroids, chemotherapy, radiation therapy
- Discontinuation of sex steroids, vitamins A and D and milk and alkali
- Appropriate management of other underlying disease states (see section on causes of hypercalcemia)

interventions—such as pinning of fractures rather than casting—would go a long way in establishing a successful and safe schedule of mobilization.

Measures for Lowering Serum Calcium Concentration

These measures involve either increasing removal of calcium from ECF (enhancing urinary or dialysis loss of calcium and increasing skeletal calcium sequestration) or decreasing entry of calcium into ECF (reducing skeletal calcium mobilization and decreasing intestinal calcium absorption).

Enhance Calcium Loss Through Urinary Excretion or Dialysis

A number of physiological maneuvers that reduce the renal reabsorption of sodium also affect the renal handling of calcium in a similar manner.[428,475] Kleeman and associates[476] found that an increase in sodium intake from 25 to 350 mEq per day in a normal man leads to a threefold increase in urinary calcium excretion. The correlation of sodium and calcium clearance is not directly related to changes in glomerular filtration rate (GFR) since, when GFR is increased by means other than sodium infusion, there is only a slight increase in calcium excretion.[477] A dramatic increase in urinary excretion of calcium may result from sodium diuresis induced by the simultaneous infusion of saline and administration of furosemide (Lasix®) or ethacrynic acid (Edecrin®). The augmentation of calcium excretion by this method has been used successfully in the management of hypercalcemia.[478] Furosemide administration also diminishes the hypercalcemic response of rats to dihydrotachysterol when both agents are given simultaneously.[479] Saline should first be given to restore ECF volume as gauged by clinical measurements and by central venous or pulmonary wedge pressure. An additional 1 to 2 liters of saline solution may then be administered before beginning administration of furosemide, which should be given intravenously in doses of 100 to 200 mg at intervals of one to two hours to maintain urinary volume above 500 ml per hour. Urinary fluid losses should be meticulously replaced on a volume for volume basis. Saline and 5 percent dextrose in water administered in a ratio of 3:1 or 4:1 with 20 to 40 mEq of potassium chloride and 10 to 20 mg of magnesium ion per liter of infusate would be adequate for replenishing initial electrolyte losses.[480] Subsequent replacement therapy may be guided by the periodic measurement of urinary concentration of these ions. Figure 16, reproduced from Coburn, Brickman and Massry,[480] illustrates the management of a patient with hypercalcemic crisis using saline loading and intravenously given furosemide. The use of 30 liters of intravenously given fluid over a period of 28 hours underscores the critical necessity of intensive clinical and laboratory monitorings. When rightly and adequately carried out, the main advantage of this form of therapy is the relative freedom from side effects. In our experience, the calcium-lowering action of this form of therapy is variable and not uniformly effective. Its effectiveness may also diminish after a few days.[481] Ong and associates[482] found that although significant calciureses were observed in both acute and chronic furosemide administration

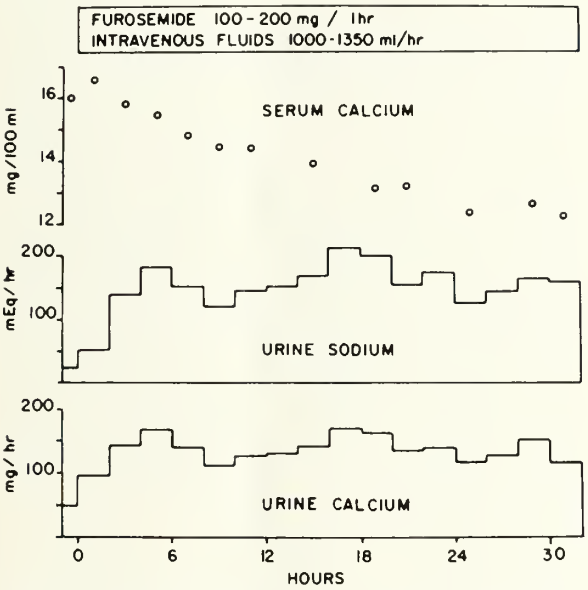

Figure 16.—The use of saline loading and large doses of intravenous furosemide for the management of a patient with acute hypercalcemic crisis. Over 28 hours of such therapy, the patient received a total of 30 liters of fluid intravenously (1.07 liters per hour), with 22.5 liters of 0.9 percent saline, 7.5 liters of 5 percent dextrose and water containing a total of 840 mEq of potassium chloride (approximately 80 mEq per liter) and 560 mg of magnesium (approximately 0.5 ml of 50 percent magnesium sulfate per liter). The urine flow rate averaged 20.8 ml per minute. Pertinent blood chemistry values at the outset and on completion of this therapy included sodium, 140 and 137 mEq per liter; potassium, 2.5 and 5.0 mEq per liter; chloride 99 and 102 mEq per liter; bicarbonate, 27.5 and 28 mEq per liter; creatinine, 1.0 and 0.8 mg per dl; magnesium, 1.20 and 1.48 mg per dl, and phosphorus, 2.45 and 2.40 mg per dl, respectively. [Reprinted from Coburn, Brickman and Massry[480] with permission.]

in dogs, decreased plasma calcium levels occurred only in acute studies. The reason for this observation was unclear, although intermittent dehydration during the course of chronic diuresis was considered a possible explanation. In patients with oliguric renal failure and congestive heart failure, this form of therapy is clearly unsuitable. These considerations, together with the great demand on medical and nursing effort, render this therapeutic modality less popular than one would anticipate.

Other measures that increase urinary calcium excretion listed in Table 4 are now only infrequently used in clinical practice. EDTA[483] increases urinary calcium excretion by forming with calcium soluble, filtrable and largely nonreabsorbable complexes. By chelating the calcium in blood, EDTA also directly reduces the ionized calcium concentration. Each gram of disodium EDTA binds about 216 mg of calcium. Goldsmith recommended a dose of 50 mg per kg of body weight administered intravenously over four to six hours.[484] Others[485] used 90 to 100 mg per kg of body weight per day to a maximum of 6 grams given intravenously over four hours. Serious side effects include hypotension and renal failure.[486,487] This form of therapy is now only infrequently used. Myers recommended this as an emergency measure only when the use of intravenous phosphate is precluded.[488]

Isotonic sodium sulfate and sodium citrate infusions have also been used for their calciuretic effect.[112,484,489,490] The increase in urinary calcium excretion is probably attributable to the associated natriuresis although the possibility of both substances acting as calcium complexing agents with subsequent urinary excretion has also been proposed. Clinical response to the use of these agents is inconsistent and unsustained. Citrate is metabolized after administration, rendering its effect even more difficult to regulate.[490] Serious electrolyte disturbances including hypernatremia (concentration of sodium is 240 mEq per liter in isotonic sodium sulfate solution) and potassium and magnesium depletion may result from injudicious administration.[491-493]

Finally, both hemodialysis and peritoneal dialysis[494-498] may be effective for rapid removal of calcium from extracellular fluid, especially in patients with oliguric renal failure and congestive heart failure. However, these are only short-term, emergency measures and generally require the concomitant institution of more definitive therapeutic measures.

Increase Net Movement of Calcium Into Bone

- *Decrease movement of calcium from bone into* ECF

Calcitonin, the hypocalcemia-inducing, hypophosphatemia-inducing polypeptide hormone, has been used in the treatment of various forms of hypercalcemia.[499-505] Its hypocalcemic action is attributed mainly to an inhibition of bone resorption. Of the three species of calcitonin (porcine, human and salmon), that derived from salmon is the most potent form known and also has the longest duration.[499,506] Calcitonin must be administered either intramuscularly or intravenously. The usual doses employed vary from 20 to 640 MRC units every 6 to 12 hours for periods up to three to four days.[480] Silva and Becker[500] used 8 MRC units per kg of body weight every six hours. The therapeutic effect of calcitonin in hypercalcemia has generally been moderate and unsustained. The development of resistance to the calcium-lowering action of calcitonin has been variously attributed to antibody formation,[507] secondary increase in PTH secretion[508] and the cellular "escape phenomenon."[509-511] Isolated case reports suggest that such resistance may be averted or ameliorated by the concomitant use of phosphate[512] or prednisone[513] It is clear that the full potential of calcitonin as a clinical agent for lowering serum calcium concentration is incompletely explored. Further systematic studies are clearly warranted since the administration of this agent is almost free of side effects. Nausea and vomiting may sometimes occur.

Mithramycin is an antibiotic derived from an actinomycete culture belonging to the genus streptomyces. It is a potent antineoplastic agent, useful in the treatment of testicular malignancies. The hypocalcemic effect of mithramycin was first observed in normocalcemic patients treated for testicular tumors and, subsequently, in hypercalcemic patients with neoplasia.[514] Since then, mithramycin has been used in the treatment of patients with hypercalcemia of different causes.[515-518] It probably acts like actinomycin D—by forming a complex with DNA in the presence of magnesium or other divalent cations, thereby inhibiting DNA-directed RNA synthesis.[519] The calcium lowering action of mithramycin is attributed to this inhibition of RNA synthesis leading, secondarily, to a

state of osteoclastic refractoriness to PTH (and possibly to other bone resorption stimuli) and consequent reduction in bone calcium mobilization.[520] Parsons, Baum and Self[521] also raised the possibility of an induced state of vitamin D-resistance. However, these authors and others[522] were unable to reverse or block the calcium-lowering effect of mithramycin by giving large doses of vitamin D. Godfrey suggested a dose schedule of 1 to 2.5 mg of mithramycin in 1 liter of 5 percent glucose in water administered intravenously over three hours.[517] A course of therapy consists of daily administration on three successive days. Subjective improvement occurs within 12 hours and lowering of serum calcium concentration is seen by 36 hours. Serum calcium concentration may remain under adequate control for as long as 10 to 14 days before repeated administration of mithramycin becomes necessary. Perlia and associates[518] suggested a single direct intravenous injection of 25 μg per kg of body weight. This dose is repeated if no detectable lowering of serum calcium concentration is noted by 24 to 48 hours, or if the previously lowered calcium is again out of control.

Nausea and vomiting are frequent side effects. Godfrey believed these side effects could be ameliorated by slow administration over three hours and by appropriate use of prochloroperazine (Compazine®).[517] Other side effects of mithramycin include hemorrhagic disorders and renal and hepatic damage.[522] Rare complications include sudden arterial occlusion[523] and toxic epidermal necrolysis.[524] Most of the serious complications occur with more chronic and greater cumulative dose administration of mithramycin for its antitumor effect. When used cautiously and conservatively as recommended, mithramycin has so far proved to be a relatively safe and effective calcium-lowering agent.[517,518,525]

The calcium-lowering action of glucocorticoids (GC) in the treatment of hypercalcemia is still incompletely defined, both in terms of their efficacy and their mechanism of action. Originally, cortisol administration was used in the differential diagnosis of parathyroid and nonparathyroid forms of hypercalcemia.[526] The former was considered steroid-resistant and the latter steroid-sensitive. Subsequently, several cases of hyperparathyroid hypercalcemia responsive to GC therapy[527-530] and numerous cases of nonparathyroid hypercalcemia insensitive to GC therapy[531] have been reported. Even in sarcoidosis, hypercalcemia may either fail to respond to GC[370,382,526,532] or takes an unusually long time to do so.[533]

Harrison and Harrison,[534] in 1960 showed an "antagonistic" effect of GC on vitamin D-mediated calcium absorption in experimental animals. Subsequent studies by Sallis and Holdsworth[535] lend further support to the thesis. Kimberg and associates,[536,537] however, provided evidence suggesting that GC inhibits intestinal calcium absorption through a process not directly related to vitamin D metabolism. In practical terms, reduction in intestinal calcium absorption *per se* is unlikely to have a substantial effect on the correction of hypercalcemia except in cases characterized by excessive calcium absorption. Even under such circumstances, the net effect will not be expected to exceed that of simple dietary calcium restriction.

Since glucocorticoids are also known to exert direct action on bone and kidney, the possibility of some extraintestinal calcium-lowering action should also be considered. Jee and associates[538] suggest, based on data from studies on rats, that GC, when administered in high doses, can cause sufficient inhibition of osteoprogenitor cell (cells which give rise to osteoclasts and osteoblasts) proliferation to result in a reduction in the pool-size of both osteoclasts and osteoblasts. Others[539,540] have shown that brief treatment of isolated bone cells with GC *in vitro* may lead to an inhibition in RNA and protein synthesis. The direct inhibitory effect of GC on bone cell activity may account for some of its calcium-lowering actions in various hypercalcemic disorders including isolated cases of hyperparathyroidism.[527-530] Myers[255] suggested that the lack of calcium-lowering action of GC in hyperparathyroid patients may be attributed to an insufficient dose of GC used. In terms of its action on the kidney, long-term GC administration is known to augment urinary calcium excretion in both animals and man.[541-543]

In the treatment of neoplasia hypercalcemia, glucocorticoids have been considered highly effective by some[544,545] and singularly ineffective by others.[531] Most authors considered the calcium-lowering action of GC a secondary phenomenon to a primary action on tumor growth inhibition[546,547] However, a direct action of GC on bone[545,548] cannot be clearly excluded. Recent studies also indicate that GC may inhibit either prostaglandin synthesis[549] or prostaglandin release.[550]

GC may be given either orally or parenterally, usually in divided doses. Goldsmith[481] suggested a dosage of 150 mg of cortisone per day. Ajlouni and Rosenfeld recommended prednisone, 60 to 80 mg per day, or its equivalent initially, followed by gradual reduction to the lowest controlling dose.[551] In the treatment of cancer hypercalcemia, Buescu and associates advocated 300 to 400 mg of hydrocortisone per 24 hours.[485] The calcium-lowering effect of GC may take a week to develop. The side effects of steroid therapy are well known—not the least of which are the catabolic and infectious complications which may seriously compound the problems in an already debilitated hypercalcemic patient. If glucocorticoids are utilized as urgent therapy for short periods (days), the author (CRK) advocates the use of very large doses (80 mg or more per day of prednisone or its equivalent).

The use of prostaglandin synthesis inhibitors in correcting some tumor hypercalcemia has already been discussed. The recommended dosages for indomethacin and acetylsalicylic acid are 75 to 150 mg and 1.8 to 4.8 grams per day, respectively, in divided doses for five to seven days.[84] This modality of treatment should still be considered experimental. Possible untoward side effects of both indomethacin and acetylsalicylic acid have not been fully characterized.[95-97] The use of propranolol in the management of thyrotoxic hypercalcemia[249] likewise should remain, for the moment, a research endeavor.[552] The importance of optimal mobilization in the management of hypercalcemia has already been discussed.

Another therapeutic measure to inhibit calcium mobilization from bone is proposed by Gallagher and Nordin.[553] These authors reported the use of ethinylestradiol in ten postmenopausal hyperparathyroid patients. They observed a gradual fall in both fasting levels of plasma and urine calcium and 24-hour urine excretion of calcium and hydroxyproline. They therefore proposed that estrogen treatment of these patients may prevent bone disease by inhibiting bone resorption and stone disease by reducing urinary calcium excretion.

- *Increase movement of calcium from* ECF *into bone*

Over four decades ago, Bulger and associates first observed that oral administration of inorganic phosphate decreased the hypercalcemia in patients with hyperparathyroidism.[554] Subsequently, the efficacy of this agent in the treatment of hypercalcemia of various causes has been repeatedly confirmed.[555-558] The administration of inorganic phosphate to hypercalcemic patients is associated with a fall in serum calcium levels, a reduction in urinary calcium levels and a positive calcium balance. These effects of inorganic phosphate are probably due to a net movement of calcium and phosphate into the skeleton.[559] Rasmussen and Bordier[560] summarized data suggesting that *in vivo* phosphate acts by stimulation of osteoblastic activity. However, Raisz and Niemann,[561] in studies on the effect of phospate upon the responses of bone cell cultures *in vitro,* found that an increasing phosphate concentration in the medium not only increases the rate of bone formation but also decreases the rate of resorption.

Inorganic phosphate may be administered orally, intravenously and, on occasions, rectally as a retention enema. As a general rule, the oral (or rectal) route, rather than the intravenous route, should be used except in those instances when rapid lowering of serum calcium is clearly a lifesaving measure. The recommended dose of intravenous phosphate is 50 mmole (1.5 grams) of phosphorus over six to eight hours.[562] Only one dose should be given in a 24-hour period and generally no more than two doses are necessary. Serum calcium may fall within minutes after the initiation of infusion and the maximum decline may be delayed for as long as five days after the completion of the infusion. Some effects may persist for as long as 6 to 15 days.[557-562] Oral phosphate therapy is usually initiated at a dose of 1.0 to 1.5 grams of phosphorus per day in divided doses. If no substantial drop in serum calcium is observed in about three days, the daily dose can be increased by 0.5 to 1.0 gram at intervals of two to three days until a total daily dose of 2 to 3 grams is reached. Normal serum calcium levels are usually achieved within one to ten days after a cumulative dose of 1 to 20 grams.[480,562] The duration of oral therapy may range from 2 to 119 days with a cumulative amount of phosphate from 3 to 214 grams.[557] Some of the commercially available phosphate preparations are listed in Table 5.

One of the most serious side effects of inorganic phosphate administration is the possible occurrence of extraskeletal precipitation of calcium.[556-563] Because soft tissue calcification can be found in untreated hypercalcemic patients, in clinical practice it has been difficult to determine

TABLE 5.—*Commercially Available Phosphate Preparations*

Preparations	*Quantity Containing 1 gram Phosphorus*	*Other Electrolytes with Each 1 gram Phosphorus*	
		Na (mEq)	*K (mEq)*
Intravenous			
In-Phos® (Davies, Rose-Hoyt)	40.0 ml	65.0	8.0
Hyper-Phos-K® (Davies, Rose-Hoyt)	15.0 ml	....	50.0
Oral			
Fleet's Phospho Soda® (C.B. Fleet Co).	6.2 ml	57.0	....
Neutra-Phos® (Willen Drug Co.)	300.0 ml or 4 capsules	28.5	28.5
Neutra-Phos-K® (Willen Drug Co.)	300.0 ml or 4 capsules	....	57.0
Phos-Tabs® (Davies, Rose-Hoyt)	6 tablets	....	57.0

if such calcification is produced or aggravated by phosphate administration. Laboratory studies, however, have shown that inorganic phosphate treatment of hypercalcemia leads to calcium deposition in the heart, kidneys and other tissue.[567] Oral phosphate administration in experimental hypercalcemia has been shown to accelerate calcium sequestration in soft tissue.[568] In one study, only those rats treated with phosphate died. Extensive soft tissue calcification has also been described in rabbits given oral phosphate therapy.[569] Other serious complications associated with clinical use of inorganic phosphate include hypocalcemia, hypotension and renal failure.[565,570-572] Complications are more apt to develop when phosphate is given intravenously (especially in excessive amounts or with too great a speed), or when it is given to patients with impaired renal function. In patients with poor renal function, no more than 0.5 to 1.0 gram of phosphorus given intravenously or 1 gram of phosphorus given orally should be administered over 24 hours.[562] Therapy should be discontinued or doses greatly reduced if serum phosphorus levels rise above 6.0 mg per dl.[480] When cautiously and appropriately used, inorganic phosphate is an effective agent for the control of both acute and chronic hypercalcemia. Aurbach and associates,[150] for example, found short-term (one to ten weeks) orally given neutral phosphate an excellent agent for both halting rapidly worsening hypercalcemia and preparing patients with severe hyperparathyroidism for surgical operation. The only complication they encountered was hypokalemia which responded rapidly to orally given potassium supplement. They did caution against long-term oral administration of phosphate.

Decrease Intestinal Calcium Absorption

The role of corticosteroids in reducing intestinal calcium absorption has already been discussed. Reduced oral calcium intake would rationally constitute the first step in decreasing net absorption of calcium from the gastrointestinal tract. In practice, this measure is maximally useful in conditions in which gastrointestinal calcium hyperabsorption contributes substantially to the development of hypercalcemia—for example, high calcium intake, sarcoidosis, vitamin D intoxication and idiopathic hypercalcemia of infancy. Of theoretical interest, but little practical application, is the use of calcium-binding agents as a means of reducing intestinal calcium absorption. These include oxalate (rhubarb, alfalfa), sodium phytate (cereals) and cellulose phosphate.[484] Both phytate and cellulose phosphate are also hydrolysed to a variable extent in the intestine, releasing inorganic phosphate, the absorption of which may contribute to the reduction of hypercalcemia.

Summary on Modalities for Lowering Serum Calcium Concentration

As has already been emphasized, every case of hypercalcemia should receive general supportive measures which essentially consist of adequate rehydration with normal saline, maximal tolerated mobilization, and reevaluation of the need and dosage of the current medications. The need to institute aggressive measures to lower serum calcium levels depends on the presence or absence of overt biological disruptions which, in turn, generally depend on the severity and rapidity of the development of hypercalcemia. When immediate lowering of the serum calcium concentration is not clinically mandatory, modalities such as orally given furosemide with adequate salt supplements, corticosteroids, and orally given phosphates may be considered. In acute emergencies, patients should be immediately kept under intensive care surveillance while simultaneously receiving saline loading coupled with parenteral furosemide. In patients with oliguric renal

failure and congestive heart failure, peritoneal dialysis or hemodialysis constitutes the alternate modality. Calcitonin is always a worthwhile additional therapy for the first 12 to 24 hours during which time a more definitive management strategy is formulated. Therapy with corticosteroids, if not otherwise contraindicated, should be started as soon as possible. In severe primary hyperparathyroidism with hypophosphatemia, careful intravenous phosphate administration, until the establishment of effective oral phosphate therapy, is an acceptable approach. Surgical operation, of course, should be planned and carried out as soon as the patient is ready. In most of the neoplasia hypercalcemia, mithramycin administration according to the recommended schedule is a safe and frequently effective therapy. There is now probably sufficient empirical observation to justify the additional use of prostaglandin synthesis inhibitors in desperate cases. All these measures are, of course, only preparatory maneuvers for stabilizing the patient for more definitive therapy of the primary cause. Therefore, the use of these measures in a patient in whom severe hypercalcemia is clearly one of the terminal events is probably ill-advised in many instances.

Measures for Correcting Primary Causes

Of the measures listed in last section of Table 4, only that of parathyroidectomy in asymptomatic hyperparathyroidism will be further discussed. With the discovery of increasing numbers of patients with asymptomatic or biochemical hyperparathyroidism, the question of indication and timing for surgical therapy naturally arises. An argument against routine operations in these patients are the reported[136-138] and unreported cases of patients with untreated hyperparathyroidism who lived for many years without ever becoming symptomatic or having any overt deterioration develop. Moreover, surgical operation in mild and early hyperparathyroidism is technically difficult. Inadequate surgical operation would render the urgently needed subsequent operation even more problematic and an inappropriate operation may lead to the development of permanent hypoparathyroidism.

We feel the available data justify the position that surgical therapy should be considered in all patients in whom a firm diagnosis of primary hyperparathyroidism is made. Many so-called asymptomatic patients may have adapted to their symptoms which become apparent retrospectively only after their alleviation following surgical therapy.[39] The subtle increase in blood pressure in asymptomatic hyperparathyroid patients has already been mentioned.[157] Although these subjects may not be overtly hypertensive, in all 15 patients in whom reinvestigation was carried out after parathyroid surgical operation, a decrease in both serum calcium and blood pressure levels was consistently observed. Kaplan and associates[573] showed in many "asymptomatic" hyperparathyroid patients slight impairment in renal function and significant physiologic derangements such as negative calcium balance, hypercalciuria, low bone density and intestinal hyperabsorption of calcium—which were all corrected by parathyroidectomy. The very observation that most early cases are relatively asymptomatic is by itself a good reason for curative therapy since primary hyperparathyroidism in clinically recognizable states is associated with a wide variety of morbidities. The hazard of normocalcemic hyperparathyroidism culminating in hypercalcemic crisis has also been reported.[497] Finally, in a prospective study of the natural course of asymptomatic and uncomplicated primary hyperparathyroidism, surgical therapy was required in approximately 20 percent of these patients by the end of five years because of progression of the disease.[574] No identifiable criterion or combination of criteria was useful in selecting outpatients in whom, in the course of follow-up, surgical intervention would be required. Moreover, the authors stated that adequate follow-up of patients with "biochemical" hyperparathyroidism was ". . . time consuming, expensive and, at times, extremely taxing. With time, asymptomatic patients tend to discount the potential seriousness of their disease and drop out of follow-up, despite heroic efforts to bring them back." As a result, these authors now recommend surgical treatment "whenever the patient does not express interest and great willingness to participate in a prolonged period of systematic and regular observation."

Surgical procedures in the parathyroid glands should always be done by surgeons specifically trained for the task. Size, shape, color, number, location and circulation of normal and abnormal parathyroid glands vary enormously.[575-578] When parathyroid surgical therapy is meticulously carried out by an experienced surgeon, the cure rate for first-look neck exploration is well over 90 percent.[579] Autotransplantation of some hyperplastic parathyroid tissue to a more accessible

intramuscular site at the time of operation has received much discussion recently[580,581] but its definitive role remains to be defined. Finally, Doppman and associates[582] reported their experience with embolic infarction of ectopic parathyroid glands located by arteriography in three patients after unsuccessful surgical operation. Two mediastinal adenomas were successfully infarcted, one with apparent cure of the patient.

CONCLUSIONS

- Total serum calcium concentration consists of protein-bound calcium (40 percent), diffusible calcium complexes (10 percent) and ionized calcium (50 percent). Elevation in ionized calcium levels is usually, but not always, reflected by the total serum calcium concentration.
- The maintenance of body fluid calcium concentration is accomplished jointly by two basic physiological processes: ECF-bone mineral flux and renal calcium reabsorption. A coordinated resetting of ECF-bone equilibrium and renal threshold for calcium reabsorption can perpetuate a stable or equilibrium hypercalcemic state with little or no continued loss of calcium. This is in pronounced contrast to the unstable or disequilibrium form of hypercalcemia which is characterized by accelerated net bone resorption with consequent outpouring of large quantities of calcium into ECF. Renal calcium reabsorption capacity becomes rapidly saturated and a large excess of calcium is excreted.
- Neoplasia is the most frequent cause for hypercalcemia seen in hospital patients. In contrast, primary hyperparathyroidism is by far the most common underlying cause for hypercalcemia encountered in the general population. There is evidence suggesting that primary hyperparathyroidism and malignancy may co-exist more frequently than could be expected by chance.
- Awareness of the clinical correlates and the natural history of various hypercalcemic syndromes, coupled with skillfully elicited history and physical examinations, continues to play a crucial role in the correct diagnosis of the causes of hypercalcemia in clinical practice.
- Management of patients with hypercalcemia should commence with the restoration of fluid and electrolyte balance. Measures toward lowering ECF calcium concentration include physiological and pharmacological maneuvers aimed at increasing removal of calcium from ECF (increasing urinary excretion, removal through dialysis and bone mineral sequestration) or decreasing addition of calcium into ECF (reducing bone mineral mobilization and intestinal calcium absorption). The implementation of such measures would allow time for complete diagnostic workup and the institution of definitive treatment for the underlying cause.

Addendum

Two important areas of hypercalcemic disorders were inadvertently omitted. The entity familial hypocalciuric hypercalcemia has most recently been reviewed by Marx and associates (Am J Med 65:235-242, 1978). The central and the peripheral neurotoxicity of parathyroid hormone has received considerable attention in recent years (J Clin Invest 55:738-745, 1975; J Clin Invest 62:88-93, 1978).

Since the completion of the present review a number of new articles have also come to our attention: "Increase in Serum Ionized Calcium During Exercise" (Clin Sci Molecular Med 53: 579-586, 1977); "Hypercalcemia in Patients with Burkitt's Lymphoma" (Am J Med 64:691-695, 1978); and "The Possible Association Between the Development of Parathyroid Adenoma and Previous Head-and-Neck Radiation" (Ann Intern Med 88:804, 1978; and Ann Intern Med 89: 216-217, 1978).

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Important Advances in Clinical Medicine

Epitomes of Progress — Otolaryngology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in otolaryngology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in otolaryngology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Otolaryngology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

BSER Audiometry

BRAIN STEM EVOKED RESPONSE (BSER) audiometry is the term for the clinical use of averaged auditory evoked potentials recorded from the human scalp up to 10 msec after the auditory stimulus.

The early evoked response consists of several waves which have been numbered by Roman numerals. Wave V is the most prominent and is used for clinical study. The origin of wave V is thought to be in the region of the inferior colliculus. The latency of wave V decreases with an increase in the intensity of the stimulus and can be recorded to levels within 10 dB of threshold. The early evoked auditory response is not altered by level of attention or sedation.

Latency/sensation level functions have been established for persons whose hearing is within normal limits and are remarkably constant in different settings. A conductive hearing loss is shown by an increase in the latency of wave V at all sensation levels of the stimulus. A sensorineural hearing loss with recruitment is characterized by increased latency of wave V near threshold with normal latency at higher stimulus intensity levels.

For site of lesion studies, the latency between wave I and wave V is also measured. Wave I is thought to represent the surface recorded cochlear nerve action potential. A brain stem disorder is characterized by an increase in neural conduction time; wave I occurs within the normal latency while wave V is delayed.

Clinically, BSER auditometry is being used to determine auditory thresholds for very young children or those who are difficult to test, as well as for patients with functional hearing loss. Brain stem lesions such as cerebellopontine angle tumor, multiple sclerosis or brain stem vascular and neoplastic lesions may be identified with the use of the I-V intrawave latency.

JANNA SMITH LANG, PhD

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Picton TW, Woods DL, Baribeau-Braun J, et al: Evoked potential audiometry. J Otolaryngol 6:90-119, 1977

Brain Stem Electric Response Audiometry

EARLY DIAGNOSIS of hearing impairment in children is extremely important. The sooner a loss is discovered and treatment begun, the better the outlook for rehabilitation.

Until recently there was no reliable method of measuring hearing in infants and young children.

All tests depended on subjective responses to a tone or noisemaker.

Now, with brain stem audiometry, it is possible to measure hearing accurately even in the newborn. The basic principle involves the measurement of minute responses that arise in the auditory pathways in the brain stem as a result of sound stimulation. These impulses, measured with scalp electrodes, are fed into a computer which extracts the responses while cancelling interfering background electrical activity.

The test is objective, requiring little cooperation on the part of the child. Best traces are obtained with a sleeping child and sedation is often used.

Whenever the parents or the doctor suspects a hearing loss, the matter should be pursued until a conclusion regarding hearing level is reached. Brain stem audiometry, an office procedure requiring approximately one hour, now enables hearing specialists to arrive at a diagnosis and begin appropriate therapy. This technique represents a significant advance in the field of otolaryngology.

DERALD E. BRACKMANN, MD

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Closure of Facial Wounds

THE CLASSICAL CLOSURE of facial wounds includes a meticulous subcutaneous closure most commonly done with an absorbable suture and then a careful subcuticular or epidermal skin closure, usually done with nylon. The subcuticular closure is time consuming and unless done well does more harm than good. The interrupted epidermal closure with 6-0 nylon can be time consuming and traumatic to the wound edges because early removal is warranted.

Recently a new suture has been described. The 6-0 Davis and Geck *mild* chromic suture comes on a small sharp CE 2 cutting needle. It is most commonly placed very superficially in the wound edges using a running locking stitch. Steristrips® are then applied. The chromic is so loosely constructed that with moisture, it dissolves in three to four days. The Steristrips are changed in four to five days and the remaining suture material pulled out with the Steristrip. For insurance, the wound is dressed with Steristrips again for an additional four or five days. Initially, a mild degree of inflammation may be present, but there is no evidence that this adversely affects healing.

This technique has been successfully used to close facial lacerations particularly in children, but also in adults. It has been used in blepharoplasties, facelifts, scar revisions, excision of skin tumors with local flap closures and to close a myriad of other wounds. The results have been as good as with any other type of closure, while postoperative trauma to the wounds has been lessened and the amount of time spent by surgeons in each procedure reduced.

TERRENCE M. DAVIDSON, MD
ALAN M. NAHUM, MD

REFERENCE

Webster RC, Davidson TM, Smith RC: Practical suggestions on facial plastic surgery—how I do it. Laryngoscope 86:1280-1284, Aug 1976

Epiglottitis: Intubation Versus Tracheotomy

INNOVATIONS IN MEDICAL THERAPEUTICS frequently lead to controversy. Successes with new techniques frequently cause physicians to eliminate other effective alternative forms of treatment which have been proven successful. In an unpredictable disease such as epiglottitis the ability to use alternative methods of treatment will yield a higher success rate.

For the past few years intubation for instituting an artificial airway has replaced tracheotomy in many centers for the treatment of supraglottitis. Many reasons are given for this change, including the following: intubators are more readily available than experienced tracheotomy surgeons, nursing is more readily available to care for intubated children than for tracheotomized children, a higher complication rate has been reported when tracheotomy is done, and earlier decannulation with intubation and shorter hospital stays have been reported when intubation is done rather than tracheotomy.

To critically analyze the effectiveness, complications and mortality of tracheotomy as the sole form of treating the airway problem in epiglottitis, a 20-year study was undertaken which included all patients admitted to Childrens Hospital of Los Angeles for treatment of this disease.

During the study, 1957 to 1977, a total of 170 patients with epiglottitis were treated by tracheotomy. Not a single death occurred in the group studied. Of the 147 patients whose charts were available for this study no serious complications

occurred. The median range of the hospital stay after tracheotomy was six to seven days. With the protocol of treatment as seen in a setting such as Childrens Hospital of Los Angeles, tracheotomy is a safe method of treatment of the airway problem associated with epiglottitis.

Cantrell and co-workers reviewed 740 cases of epiglottitis recorded in the literature. Of these, 348 (46.5 percent) were treated with tracheotomy, 216 (28.8 percent) with intubation and 214 (24.7 percent) with observation. The highest mortality rate (6.1 percent) occurred in the group of patients treated with observation. Mortality in the tracheotomized patients was 0.86 percent, while in the intubated group it was 0.92 percent.

The controversy, therefore, is not whether tracheotomy or intubation is the treatment of choice, but rather whether conservative measures with observation is ever indicated in this most unpredictable of infectious disease of the larynx. The choice of establishing the airway should be determined by the availability of adequate facilities in the institution in which the child receives care. A team comprised of a pediatrician, an anesthesiologist and an otolaryngologist is essential in the treatment of a child with epiglottitis.

Establishment of an airway whether by tracheotomy or endotracheal intubation is mandatory in the treatment of this disease. A tracheotomy may be necessary in some children because of difficulties encountered with intubation, or when complications of intubation may have occurred.

SEYMOUR R. COHEN, MD

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Cantrell RW, Bell RA, Morioka WT: Acute epiglottitis: Intubation versus tracheotomy. Trans Pac Coast Otoophthalmol Soc 57:75-89, 1976

Freeze-Dried Ear Transplants

FREEZE-DRYING is a useful technique for the preparation and preservation of bone and fibrous tissue transplant parts. There is minimal alteration of the tissue with this procedure. Compelling evidence shows that freeze-dried allograft tissue serves as a reliable template for creeping substitution or replacement by the recipient.

The middle ear transformer mechanism can be reconstructed like-part for like-part with freeze-dried otologic transplants. The advantage of this to the surgeon is the ease of availability of the tissue, which can be stored in small containers in any hospital at room temperature. The simplicity of its use also is attractive. Foreign body extrusion, that has been prevalent with the use of various plastics and metals, is avoided with freezed-dried material.

Freeze-dried dura periosteum, fascia and fibrous tympanic membrane are widely used for the repair of fibrous tissue defects in paratemporal bone lesions.

MANSFIELD F. W. SMITH, MD

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Invasive Radiology In Head and Neck Surgical Operations

RECENT ADVANCES in invasive radiology have added new dimensions to management of vascular lesions of the head and neck. Percutaneous arterial embolization, originally used for thrombosis of arteriovenous malformations, has now been successfully used in the treatment of vascular neoplasms and hemorrhagic disorders. The technique involves the selective catheterization of branches of the carotid system. Major feeding vessels are identified fluoroscopically and carefully embolized using one of various clotting methods.

The preoperative embolization of vascular head and neck tumors such as angiofibromas or chemodectomas has been beneficial in reducing operative blood loss. In addition, this technique has been useful in palliative reduction of vascularity of unresectable lesions.

The control of hemorrhage has proven to be another valuable use for this technique. Duodenal bleeding, posttraumatic pelvic hemorrhage and epistaxis have all been reportedly controlled by arterial embolization.

Many substances have been tried as clotting agents. The safest of these is autologous tissue such as clotted blood or muscle. Other materials include metal filings, absorbable gelatin sponge (Gelfoam®), silicone as liquid or spheres, and polymerizing agents. The most promising technique involves the use of a detachable balloon catheter. Because it can be inflated and deflated before detachment, it offers the opportunity to evaluate changes in flow dynamics and potential

neurological sequelae before irreversible clotting of an arterial vessel occurs.

Fortunately, complications are rare when the procedure is done by an experienced angiographer. The most life-threatening of these is thromboembolism from inadvertent clotting of a normal vessel or retrograde thrombosis from the embolized artery.

The essentials for use of percutaneous arterial embolization appear to be (1) a qualified and competent radiologist, (2) careful selection of cases and (3) strict adherence to details of technique. With these observed, the procedure can be valuable to surgeons dealing with vascular lesions of the head and neck.

JAMES N. THOMPSON, MD

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Use of Carbon Dioxide Laser Technology in Laryngeal and Pharyngeal Surgery

CARBON DIOXIDE LASERS have been developed which, when coupled to microscopes, permit precision removal of superficial lesions in the mouth or larynx. These lasers have a wave length of light which causes them to cauterize or incise any tissue on contact.

This space age technology has the advantage of delivering infrared heat to the target area in precisely controlled amounts. Furthermore, it does so without requiring the placement of a metal blade, such as a Bovie tip, on the area to be treated. This allows the effect on the tissue to be observed at all times. Because the area required for passage of the carbon dioxide laser beam is small, it can be used through modern laryngoscopes which have been designed to permit visualization of the larynx or hypopharynx while using the microscope for both magnification and binocular vision with the appendant depth perception. Furthermore, since the heat cauterizes vessels up to 1 mm in diameter, it is possible to operate in a virtually bloodless field. When larger vessels are encountered they can be cauterized, if necessary, with a conventional Bovie tip.

Carbon dioxide lasers have been in use for several years on the East Coast and now are used for ear, nose and throat procedures at the University of California, San Francisco, for conditions ranging from papilloma of the larynx and leukoplakia of the mouth to superficial cancers of the oral and hypopharyngeal membranes. They also have been used for treating superficial lesions of the cervix and for removing warts on the skin. Consideration is being given to their use in neurosurgery for small lesions, and also in general surgery for bowel papillomas.

HERBERT H. DEDO, MD

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EDITORIALS

Another Perspective on Health Care Costs

LAST MONTH a perspective on health care costs was discussed in these columns. It was pointed out that the rising costs of health care can be viewed as a measure of the real success of a national determination to develop better health care and make it more available to more people. The rise in health care costs, or that part of it that is rising faster than the costs of everything else, was viewed as a rough measure of the extent to which this has been accomplished. Elsewhere in this issue is a discussion by a well-trained American physician of his experience with medical care in Southern India. It gives one yet another perspective on health care costs—in India and in America.

In India there are physicians well trained in modern medical technology who practice good medicine and carry out skillful surgical operations but there are nowhere nearly enough of them to meet the needs of the population. There are also very great and often insurmountable problems of cost. But they are very different from ours. For example, in India there may be difficulty in paying the cost for a simple antibiotic drug or for a needed prosthetic valve to prolong the life of a patient with the all too prevalent advanced rheumatic heart disease. It is those citizens who somehow can pay costs such as these who receive treatment. The physicians and other health personnel are poorly paid by our standards. One suspects that the cost benefit of what is done is very high for those who receive treatment, and also that the overall cost of health care in India is very low—because there just is not very much of it. But then illness and death are much more taken for granted and readily accepted in India than they are in America.

By contrast our country has given a high national priority to health, health care and the postponement of death. Billions of dollars have been invested in research and the development of new, sophisticated and often costly technology. Health care has become the second largest industry in this highly industrialized nation. Charity in health care has been eliminated as demeaning to the recipients, and health professionals and other employees in the health care field have recently achieved something like parity with workers in business and industry. Our government is pressing hard to see that health care resources and personnel are more evenly distributed and that modern medicine is more equally and readily available to all our citizens. And in both public and private sectors costly efforts are being made in the prevention and early detection of disease. All of these factors increase the use of more kinds of medical and health care services. None is likely to reduce health care costs. Indeed the opposite has been the case. All of this is quite different from the situation in India.

In this perspective it appears that health care costs are as much a function of the quantity, quality and deployment of the resources available for the purpose as anything else. If availability and usage of resources is low the costs will be low, and if they are high so will be the costs. In India there is not enough money or sufficient resources and this is one kind of cost problem. Here there is concern that America is putting too much money and too many resources into health and health care and this is an opposite kind of cost problem. It is probable that each nation will get what it wants and what it is able or willing to pay for. So far America has been able and willing to pay for what it wants in health care. But the costs are real and they are great, and they are not likely to be legislated or ruled or wished away so long as the priority for health and health care in this nation is what it is.

—MSMW

Some Musings of an Aging Nail-Watcher

If, as Samuel Johnson said, the knowledge that one has got to die in a couple of days "wonderfully concentrates the mind," it is equally true that finding oneself quoted in the first and second references of an article "wonderfully relaxes the mind." One has the sense that the writer must be a wise and perceptive chap. This, of course, holds only if the quotation is not for purposes of attack or denigration. Though I long ago concluded that the effect of publishing papers of instruction and uplift in medical and scientific journals was marginal, at best, it is only by iteration and reiteration that, by a kind of literary law of mass action, certain chemical transformations may occur in the minds of the reader.

Just as the ophthalmoscope gives one a wonderful view of a vascular bed, the small vessels in the retina and thus, up to a point, a general picture of small vessels throughout the body, so indeed the nails give a ground-glass window to disease. I find it essential to established physical contact with a patient by shaking hands or some other appropriate gesture. Having taken a patient's hand in mine I then look at the fingers, the palms, the dorsum and the nails. At times one gets an altogether unexpected clue to some ancient event or some current disease or lesion.

Shearn has gathered together a series of observations and has sought out many articles and papers dealing with the nails and nail growth. This is a fine clinical summary although, as is indicated, it is highly selective and makes no claim to be anything else. Throughout the paper Shearn emphasizes the importance of the nails for internists or general physicians who have not yet been backed into the corner of superspecialization. He emphasizes the fact that a careful examination of the nails is easy, they are almost always readily available for inspection and comparisons. Patients, themselves, may have noticed abnormalities such as clubbing, a variation in color and so on, but are much more likely to notice leukonychia of the punctate variety or a blood blister from mashing or crushing the finger than they are most of the kinds of abnormalities Shearn describes.

Some of the clinical lessons available from careful inspection of the nails are suggested or mentioned by Shearn, but there are a number of others which may be commented upon briefly. I agree that splinter hemorrhages, unless they are extraordinarily numerous, are not likely to be of much significance. They appear regularly during the menstrual period in some women. Most people have them at some time or another. A sharply focused injury may readily produce a splinter hemorrhage which, in effect, is a minor variety of subungual hematoma. It is important to remember that similar linear red streaks may appear in Osler disease, hereditary hemorrhagic telangiectasia. The two can be distinguished clearly by merely examining the fingers. If the nail plate is depressed a splinter hemorrhage, which is extravascular blood, stands out more clearly because the background is pale when the blood is squeezed out. On the other hand, the telangiectatic linear red mark in Osler disease fades out completely with appropriate pressure because the blood is intravascular and can be squeezed out in the normal direction of flow.

I am not nearly as convinced as Terry was, or Shearn seems to be, that the "white nail of Terry" has any extraordinary specificity for chronic liver disease, though it certainly may be seen in various forms of cirrhosis. The common mistake made when one sees the white nail is to assume that anemia is present. There is a simple way to determine this. If the observer curls the index finger around the terminal portion of the patient's digit and constricts it, stopping the outflow of blood, the nail becomes deeply reddened. This is true even of severely anemic persons. The white nail, leukonychia totalis, however, does not manifest this increased redness because there is increased fibrous tissue between the nail plate and underlying vascular bed. The vascular markings are not visible underneath the nail.

An important but not often emphasized feature of clubbing is that in most instances, the exception being the congenital or hereditary clubbing, the nail floats on a soft almost gelatinous bed. It can be rocked around by depressing and elevating

the tip much more extensively than is true of the ordinary nail. Careful observation shows that this may be the very first sign that clubbing is developing. The return of the soft nail bed to its normal firmness is the first sign that the evoking force, such as bacterial endocarditis or a large pulmonary arteriovenous fistula, has been corrected.

It seems to me that of all the classical and long enduring physical signs of disease which we still encounter today, clubbing is one for which there is surely enough modern technical learning and skill for us to understand it. Besides the remarkable return to normal which may follow cutting of the afferent vagus nerve in the mediastinum in acute pulmonary osteoarthropathy and the fact that the blood flow in the clubbed nail is greatly increased, we have little to go on. It seems reasonable to suppose that with the forced irrigation, as it were, oxygen, energy sources and even growth hormone must be provided in overabundance to the germinal center of the nail. Indeed, the terminal portion of the finger, the pulp and the skin participate in this change.

A common finding in palmar erythema is for the redness of the terminal part of the phalanx to go around over the back and a clearly evident change in the skin over the germinal center at the base of the nail. Under such circumstances clubbing may occur but either of these changes may occur without the other.

Being able to describe and knowing some of the things that will change clubbing and osteoarthropathy leave us a long way from the desired clear understanding of the common denominator in such an array of different diseases and states in which clubbing so often occurs.

The importance of Shearn's view is that it may either instruct or nudge the memory. An often forgotten law of clinical medicine and, indeed, one which pertains to many aspects of life is that we can't use an idea if we don't have it, that we can't use knowledge that has not been made our own, and that we may look at certain evident signs but if we don't know what we are looking for we often do not see with perception and understanding what we look at. The ability to concentrate one's attention almost to the point of incandescence enables a few people ultimately to see what is clearly before them but they understand it only if they know about it.

WILLIAM BENNETT BEAN, MD
Kempner Professor and Director
Institute for the Medical Humanities
The University of Texas Medical Branch
Galveston, Texas

On the Genesis of the Clinical Manifestations of Hypercalcemic Disorders

HYPERCALCEMIA is not uncommon and it has been observed in a variety of diseases and clinical disorders. The article by Lee, Zawada and Kleeman published in this issue provides an excellent and comprehensive review of the available information on the cause, clinical manifestations and management of hypercalcemic disorders.

Despite the large number of reports on hypercalcemia, the mechanisms through which an acute or chronic elevation in serum calcium produces harmful effects are not fully elucidated. Hypercalcemia could be classified into two major categories: One is due to hyperactivity of the parathyroid glands and the second is not induced by excess parathyroid hormone. In this latter group, the blood levels of parathyroid hormone (PTH) are, in fact, low. One may then suggest that the hazards of hypercalcemia may be related to direct effects of elevation in serum calcium or to excess PTH in blood, or both. This editorial will provide a discussion of the possible pathogenetic pathways involved in the genesis of the clinical manifestations associated with hypercalcemic disorders.

First, hypercalcemia induces dehydration through its effects on renal function. Hypercalcemia inhibits the renal tubular transport of sodium and is associated with pronounced natriuresis.[1-3] In addition, it interferes with the action of the antidiuretic hormone on the kidneys[4,5] and, therefore, is associated with polyuric and enhanced renal losses of water.[6,7] The augmentation in sodium and water excretion results in dehydration and volume contraction, with all their clinical consequences. Many hypercalcemic patients present themselves with impaired mentation and, at times, they may be stuporous or even comatose. Vigorous hydration usually results in notable improvement in their clinical condition, despite modest or even no change in serum calcium levels, an observation that underscores the role of dehydration in the clinical symptomatology of these patients.

Second, it has been shown that non-PTH-induced hypercalcemia may be associated with metabolic alkalosis,[8,9] most probably due to enhanced renal tubular transport of calcium.[10] Alkalosis may reduce cerebral circulation and increase the affinity

of hemoglobin to oxygen. Both of these effects could be associated with mild to moderate cerebral hypoxia, and as such may affect the function of the central nervous system.

Third, although hypercalcemia may affect cell function by increasing its calcium content or altering intracellular to extracellular calcium ratio, such possibilities are not likely to be operative on the brain and be responsible for the aberrations in central nervous system function. The concentration of calcium in the cerebrospinal fluid changes only slightly over a wide range of serum calcium,[11] and brain calcium content studied in experimental animals does not increase in the face of chronic hypercalcemia induced by vitamin D treatment or following repeated intravenous infusions of calcium.[12]

Fourth, soft tissue calcification is not infrequent in patients with chronic elevation in serum calcium.[13] Deposition of calcium salts may disrupt both the structural and functional integrity of the organs affected.

Fifth, acute elevation in serum calcium may increase vascular resistance and induce vasoconstriction.[14,15] This effect is most probably responsible for the elevation in both diastolic and systolic blood pressure[16-18] and the alterations in renal hemodynamics[5,19] observed during acute hypercalcemia.

These observations provide various pathogenetic mechanisms for the clinical hazards of hypercalcemia. However, most of the information on the clinical consequences of chronic hypercalcemia is derived from patients with primary hyperparathyroidism. Indeed, Lee and associates provide in their review a detailed account of the clinical signs and symptoms in such patients. Their discussion implies that these derangements are related to the hypercalcemia, per se. However, the possibility that excess PTH independent of the elevation in serum calcium may also play a major role should be considered. Evidence for the toxic effects of PTH has accumulated mainly from studies in patients with renal failure and secondary hyperparathyroidism but without hypercalcemia. This information has been reviewed elsewhere.[20,21]

The neurotoxicity of PTH has been studied in some detail. Neurobehavioral abnormalities, disturbances in electroencephalogram (EEG) and peripheral neuropathy are not infrequently seen in patients with uremia.[22,23] These derangements have been attributed to as yet unidentified uremic toxins. However, recent experimental and clinical data point towards the important role of PTH in the genesis of these disturbances. In addition, patients with primary hyperparathyroidism have similar abnormalities.[24,25]

The effects of PTH on the nervous system have been studied in detail in dogs.[12,26-28] The results of these studies showed that (1) acute uremia increases the calcium content of both brain and peripheral nerves and is associated with slowing of EEG and prolongation of motor nerve conduction velocity (MNCV), (2) parathyroidectomy before the induction of uremia prevents the rise in calcium content of both brain and peripheral nerves and averts the disturbances in EEG and MNCV and (3) administration of parathyroid extract to dogs with *normal renal function* increases calcium content of brain and peripheral nerve and induces changes in EEG and MNCV similar to those seen with acute uremia; these changes were reversed after the discontinuation of parathyroid extract administration.

These observations show that the changes in calcium of brain and peripheral nerve and the disturbances in EEG and MNCV are not related to uremia, per se, but are dependent on the presence of excess PTH. The data underscore the neurotoxic effects of PTH and its role in the genesis of the dysfunction of the nervous system in uremia. Whether these effects of PTH are directly related to the elevated blood levels of the hormone or are secondary to increased calcium content of the nervous tissue or both remains unresolved. To answer such a question, one would need an experimental model with excess PTH but normal content of brain and peripheral nerve, a combination we are unable to obtain.

Further support for neurotoxic effects of PTH is furnished by a number of clinical observations. First, Alfrey and co-workers[29] found that patients with chronic renal failure, who usually have elevated blood levels of PTH, had increased calcium content of brain. Second, Cogan and associates[30] reported normalization of EEG within three months after parathyroidectomy in patients with chronic uremia. Third, unpublished observations from our laboratory showed a direct and significant relationship between percent of slow waves (less than 7 hz) of the EEG and the blood levels of PTH among a homogeneous population of dialysis patients; suppression of the parathyroid gland activity in these patients by treatment with 1,25 dihydroxycholecalciferol ($1,25(OH)_2D_3$) was fol-

lowed by normalization of the EEG. Fourth, Ball and associates[31] reported the case of a patient with dialysis dementia who improved notably after subtotal parathyroidectomy. Fifth, Allen and associates[24] studied the EEG in patients with primary hyperparathyroidism before and after removal of the parathyroid adenoma. The EEG in these patients showed similar abnormalities to those observed in uremia, and the disturbances in EEG progressively decreased following parathyroidectomy; the recordings became normal within two to three weeks after operation. Finally Avram and co-workers[32] found that MNCV is reduced in dialysis patients with elevated blood levels of PTH, while MNCV is within the normal range in age-matched dialysis patients who had notably lower blood levels of PTH.

The data presented above provide support for a cause and effect relationship between excess PTH and the disturbances of the nervous system in clinical disorders with elevated blood levels of PTH. The evidence fits a modified version of Koch's postulate: Excess PTH is present in the blood of the patients, the hormone can be assayed, administration of PTH to experimental animals induces alterations in the nervous system similar to those seen in humans with excess PTH and reduction in the blood levels of the hormone is associated with amelioration of the abnormalities.

Other data indicate that PTH may be involved in the genesis of anemia,[33-36] sexual dysfunction,[37] pruritus[38,39] and disturbances in lipid metabolism,[40] noted in states with excess PTH. It is prudent, therefore, that additional data be collected on such disturbances in hypercalcemic patients with excess PTH, and an attempt be made to dissect the role of PTH or hypercalcemia, or both, in the genesis of the clinical manifestations seen in these patients.

SHAUL G. MASSRY, MD
DAVID A. GOLDSTEIN, MD*
Division of Nephrology
Department of Medicine
University of Southern California
School of Medicine, Los Angeles

*Dr. Goldstein is a recipient of a Fellowship from the National Institute of Health No. 1F32AM05754.

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Computed Tomography:

Its Efficacy and Cost

THE INTRODUCTION and explosive development of computed tomography (CT) may rank among the medical wonders of our day. However, computed tomography is beset by fiscal problems and governmental intrusion. Even Ralph Nader has injected himself into the matter to challenge the usefulness of CT scanning in "most of the diseases for which it is used."[1] Elsewhere in this issue (Articles to Read in Other Journals) are brief abstracts of a number of relevant articles appearing in the July 1978 issue of the *American Journal of Roentgenology* which contains an extensive special section on the medical efficacy of CT.

Medical efficacy may encompass diagnostic efficacy, therapeutic efficacy and health outcome efficacy.[2] As cost considerations enter the picture, they may be assessed by cost per correct diagnosis, cost per new treatment undertaken, cost per cure or cost per year of life gained.[3] There are obvious complexities in attempting to evaluate these categories of efficacy. This is compounded by the fast pace of technological development. Body scanning times have been reduced from between two and four minutes to as little as two seconds with an accompanying improvement in image resolution and quality. A state of the art scanner may cost $750,000 and a three-year-old scanning unit may be obsolete. The problems of consequent cost and cost containment have resulted in significant governmental intervention. Certificate of Need requirements have resulted in rejection of more than 50 percent of all applications since 1976. Between June 1975 and July 1976, 190 applications were rejected.[4] Ironically, the development of a new and cheaper head scanning unit costing around $100,000 has led to further protest by governmental agencies. This protest is based on the fact that these low-cost scanners will fall below the cost levels requiring a Certificate of Need.

The entry of governmental regulatory bodies into the area of distribution of medical diagnostic modalities, into decisions regarding their efficacy and into cost control must have an impact, for good or bad, on the future of medical practice. Thoughtful physicians will be challenged to determine a role for the profession in helping to resolve the inevitable conflicts between the high costs and the promise of a high quality and effective new modality such as CT.

ROBERT B. ENGLE, MD
Department of Radiology
St. Joseph Hospital
Orange, California
Associate Clinical Professor of Radiology
University of Southern California
Los Angeles

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CASE REPORTS

Refer to: Effron MK, Rosenbaum J, Greenberg PL: Remission of acute myelogenous leukemia complicating Waldenström macroglobulinemia. West J Med 129:337-339, Oct 1978

Remission of Acute Myelogenous Leukemia Complicating Waldenström Macroglobulinemia

MARC K. EFFRON, MD
Boston
JAMES ROSENBAUM, MD
PETER L. GREENBERG, MD
Stanford, California

THE DEVELOPMENT of acute myelogenous leukemia (AML) in patients with independent hematopoietic disorders has been well documented and recently reviewed.[1] In more than 70 reported cases, multiple myeloma has developed in patients with AML.[2-5] In most of these cases, the leukemia was preceded by chemotherapy with alkylating agents. AML has also been described in six patients with Waldenström macroglobulinemia,[6-11] a disease similar to multiple myeloma. Before AML developed, five of these patients received chemotherapy for the gammopathy.

The acute leukemia complicating multiple myeloma or Waldenström macroglobulinemia has generally been refractory to treatment. In our review of the literature, 36 of 74 multiple myeloma patients with AML received antileukemic chemotherapy, with achievement of complete remission in only one patient.[12] Of the six patients with AML complicating Waldenström macroglobulinemia, three died without antileukemic treatment[6,8,9] and three underwent induction therapy with failure to achieve complete remission.[7,10,11]

In this report we describe attainment of complete remission from AML in a patient with Waldenström macroglobulinemia.

Report of a Case

A 42-year-old asymptomatic white man had blood which was found to be difficult to crossmatch for blood donation in 1963. Laboratory values included a hematocrit of 37 percent and a leukocyte count of 5,600 per cu mm. Rare atypical lymphocytes with plasmacytoid characteristics were noted in the peripheral smear. Serum protein electrophoresis showed a sharp M-component spike of 2.8 grams per dl. Utracentrifugation showed a pronounced increase in 19S macroglobulins. Bone marrow examination showed a normal myeloid-erythroid ratio, normal myelopoiesis, and a pleomorphic increase in plasmacytoid lymphocytes. Results of additional studies included negative findings on Coombs, latex fixation and cold agglutinin tests. On physical examination no adenopathy, abdominal organomegaly or other abnormalities were noted. A radiograph of the chest and skeletal survey showed no abnormalities. Waldenström macroglobulinemia was diagnosed and the case was followed without treatment until 1966.

At that time, the presence of fatigue, bleeding, anemia and increasing serum IgM suggested progression of the gammopathy. Chlorambucil was administered each day for five years, to a cumulative dose of 7.3 grams. In 1971 a total of 168 mg of melphalan and 1.9 grams of prednisone was given over three months. During the following five years, the patient received 29 courses of cyclophosphamide, vincristine and prednisone (cumulative doses of 51 grams of cyclophosphamide, 217 mg of vincristine and 252 grams of prednisone) ending in July, 1976.

Over the subsequent six months, progressive pancytopenia was noted. Red cell production was decreased with simultaneously increased sequestration of ^{51}Cr-labeled red blood cells in liver and spleen. Falling platelet and erythrocyte counts

From the Department of Medicine, Stanford University School of Medicine.

Dr. Effron was the recipient of an American Cancer Society Fellowship at Stanford School of Medicine. He is now House Officer in the Department of Medicine, Peter Bent Brigham Hospital, Boston. Dr. Greenberg is a Scholar of the Leukemia Society of America.

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Reprint requests to: Peter L. Greenberg, MD, Division of Hematology, Department of Medicine, Stanford University Medical Center, Stanford, CA 94305.

were not improved by high dose steroids. A left-shifted myeloid line with reduced maturation appeared in the bone marrow. Both the immature myeloid cells and previously observed plasmacytoid lymphocytes were increased relative to other marrow elements. Small numbers of myeloblasts appeared in the peripheral blood. Serum muramidase was 24 μg per ml (normal value 5 to 10). The serum IgM, previously stable at 1.6 grams per dl, rose to 2.1 grams per dl. The patient's course was interpreted to represent early AML and increased activity of the macroglobulinemia.

In an attempt to diminish splenic sequestration of platelets and erythrocytes, splenectomy was carried out in February of 1977. Splenic histology showed an intense proliferation of myeloblasts. The leukocyte count was 5,000 per cu mm with 9 percent polymorphonuclear leukocytes, 10 percent band forms, 4 percent metamyelocytes, 26 percent myeloblasts, 52 percent lymphocytes, 3 percent monocytes, 4 percent eosinophils and 2 percent basophils; the platelet count was 14,000. In the marrow there was pronounced progression of the myeloblastic proliferation with poor myeloid maturation; a diagnosis of AML was confirmed. A 10-day course of induction therapy was carried out with daunorubicin, cytosine arabinoside and 6-thioguanine, as previously described.[13] Marrow hypoplasia was observed 14 days after treatment was begun. In addition to supportive therapy with multiple antibiotics, the patient received red blood cell, platelet and granulocyte transfusions. Three weeks after the last chemotherapy a marrow examination and a peripheral blood count confirmed complete remission with M1 status.[14] The leukocyte count was 10,600 per cu mm with 51 percent polymorphonuclear leukocytes, 13 percent band forms, 6 percent metamyelocytes, 21 percent lymphocytes and 9 percent monocytes. The hematocrit was 34 percent and the platelet count 370,000. The serum IgM was stable at 1.4 grams per dl.

Monthly doses of cytosine arabinoside and 6-thioguanine were subsequently given for maintenance therapy.[13] Three months after attaining remission, the peripheral leukocyte count was 9,000 per cu mm with 42 percent polymorphonuclear leukocytes, 10 percent band forms, 5 percent metamyelocytes, 32 percent lymphocytes and 11 percent monocytes. The hematocrit was 30 percent and the platelet count was 300,000. The patient's bone marrow was normocellular and showed normal number and maturation of hematopoietic lines. However, the marrow now also contained 60 percent plasmacytoid lymphocytes. The serum IgM was elevated to 3.2 grams per dl. Further therapy for the gammopathy was initiated. Four and a half months after attaining remission the patient's AML relapsed. The patient declined further chemotherapy.

Discussion

Acute myelogenous leukemia is recognized as a delayed consequence of antineoplastic chemotherapy, particularly when alkylating agents are used, as reviewed by several authors.[1,15-19] Reimer and co-workers have recently shown that ovarian cancer patients, if treated with alkylating agents, have an increased relative risk of AML developing.[20] An association of AML with Hodgkin disease treated by radiation with and without chemotherapy was reviewed by Rosner and Grunwald.[21] The development of AML in patients with multiple myeloma is discussed in many publications.[1-5] In a series recently reported by Gonzales, Trujillo and Alexanian the incidence of AML in melphalan-treated patients with multiple myeloma was found to be approximately 100 times higher than in normal subjects.[5] Alkylating agents have been specifically implicated as leukemogens in multiple myeloma because the increased incidence of acute leukemia in this group was not noted before the advent of alkylator therapy.[4,22] In the present case and in five of six previously reported cases of AML complicating Waldenström macroglobulinemia, alkylator treatment preceded diagnosis of leukemia.[6-10]

The AML complicating multiple myeloma and Waldenström macroglobulinemia has shown a particularly poor prognosis. Of the 36 reported multiple myeloma patients treated for AML, in only one was complete leukemic remission achieved.[12] Similarly, in the three patients with Waldenström macroglobulinemia previously given induction therapy for AML, complete remission was not reached.[7,10,11]

Despite this prior negative experience, in our patient a complete remission of the AML was obtained in the presence of Waldenström macroglobulinemia. Our successful treatment of AML is in contrast to even the most recent experience of Gonzales, Trujillo and Alexanian with six patients with multiple myeloma.[5] In our patient, activity of the Waldenström macroglobulinemia remained stable during antileukemic treatment

but began to progress three months following leukemic remission.

The reason for our successful treatment in this case is speculative. The two gammopathies may differ in their effect upon a person's ability to undergo antileukemic induction. The chemotherapy and supportive care used during induction was more intense than the treatment given in many previously reported cases of gammopathy with AML.

Mutagenesis by alkylating agents may account for leukemogenesis with this group of patients. An increased frequency of chromosomal aberrations has been noted in acute leukemias which follow alkylator treatment in myeloma patients.[5,23] Immunosuppression by alkylators may lead to leukemia. In this setting malignant clones may proliferate in a more permissive environment.

Alternatively, the increased survival of treated patients may itself enable us to observe acute leukemias developing in multiple myeloma and Waldenström macroglobulinemia. Any intrinsic predisposition to acute leukemia in these lymphoid disorders would more likely be expressed during a longer lifetime. Indeed, AML has developed in at least three cases of multiple myeloma[24,25] and one case of Waldenström macroglobulinemia[11] with no previous chemotherapy.

Coexistence in the bone marrow of two independent hematopoietic neoplasms presents potential problems for therapy. *A priori,* elimination of AML could provide a less competitive and more favorable setting for proliferation of the gammopathy. The treatment of AML involves induction of marrow aplasia with subsequent repopulation by "nonleukemic" cell lines. In the presence of Waldenström macroglobulinemia and prior chemotherapy, this preservation and replication of stem cells must take place in an altered and potentially less favorable marrow environment. However, as shown in our case, adequate stem cells are retained, and their proliferation permitted marrow regeneration.

Achievement of remission from AML in our patient with Waldenström macroglobulinemia should encourage future efforts to treat acute leukemia complicating the gammopathies.

Summary

In a patient with Waldenström macroglobulinemia acute myelogenous leukemia developed after treatment with alkylating drugs for ten years. Chemotherapy led to complete remission of the leukemia. Activity of the monoclonal gammopathy, as judged by serum IgM and bone marrow infiltrate, increased three months after leukemic remission was attained. This is the first reported successful induction of acute myelogenous leukemia in a patient with Waldenström macroglobulinemia. Although acute myelogenous leukemia complicating the gammopathies is frequently refractory to therapy, complete remission is possible.

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Acute Myelomonocytic Leukemia Following Splenectomy in a Patient With Long-Standing Hodgkin Disease

BARRY E. ROSENBLOOM, MD
ERIC J. KLEIN, MD
J. MICHAEL USZLER, MD
RICHARD ELLIS, MD
JEROME B. BLOCK, MD
KOUICHI R. TANAKA, MD
Torrance, California

THE ASSOCIATION OF acute nonlymphocytic leukemia with Hodgkin disease has been recorded in more than 100 instances.[1-4] In most of these cases the patient has had long-standing Hodgkin disease and radiotherapy has been carried out. The combination of previous radiotherapy and chemotherapy appears to further increase the risk of leukemia developing.

In a patient under our care with Hodgkin disease acute myelomonocytic leukemia developed following splenectomy for hypersplenism. The onset of acute leukemia immediately following splenectomy in a patient with Hodgkin disease has not previously been noted. In addition, because the patient's usual bone marrow sampling sites were hypoplastic, we utilized an ^{111}indium chloride bone marrow scan[5] to find a site that was accessible for aspiration.

Report of a Case

A 26-year-old man presented in June 1967 with cervical lymphadenopathy, night sweats and a 15-pound weight loss over several months. On examination diffuse adenopathy and hepatosplenomegaly were noted. A cervical lymph node biopsy study showed the presence of Hodgkin disease, nodular sclerosing type (Figure 1). Bone marrow aspirate was normal. Initially, nitrogen mustard was administered with incomplete regression (Table 1). Radiotherapy was then given, in addition to administration of chlorambucil and cyclophosphamide; apparent control was achieved. Recurrent adenopathy in 1971 led to the substitution of the MOPP (nitrogen mustard, vincristine, procarbazine, prednisone) regimen with a favorable response. After six cycles, chemotherapy was discontinued, but a lumbar spine lesion necessitated further radiotherapy to L-4. Another course of MOPP was given in 1972 and continued as maintenance every other month for 18 months. In July 1974 increasing splenomegaly and pancytopenia were noted (Table 2). Bone marrow aspirations and needle biopsy studies of each posterior iliac spine showed notably hypocellular marrow. A trial of bleomycin was not beneficial. Because of persistent pancytopenia, felt to be secondary to hypersplenism in part, splenectomy was carried out on October 29, 1974. The spleen weighed 1,100 grams and grossly nodular areas were noted. On microscopic sections there were multinucleated cells consistent with Reed-Sternberg cells (Figure 2).[6] Blood counts improved after splenectomy, but a progressive leukocytosis ensued with increasing numbers of immature forms (Table 2). A sternal bone marrow aspirate was hypocellular with a nondiagnostic pattern. On December 13, 1974, a bone marrow scan was done with ^{111}indium chloride; it showed minimal marrow function in the axial skeleton (Figure 3), but considerable activity about both knee joints

Figure 1.—Original lymph node biopsy specimen showing a pattern of noduler-sclerosing Hodgkin disease. (Reduced from ×120)

From the Departments of Medicine, Pathology and Nuclear Medicine, Harbor General Hospital Campus, UCLA School of Medicine, Torrance, California.

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Submitted, revised, December 2, 1977.

Reprint requests to: K. R. Tanaka, MD, Department of Medicine, Box 19, Harbor General Hospital, Torrance, CA 90509.

TABLE 1.—*Therapy Administered During Course of Hodgkin Disease*

Dates	*Therapy*
6/67-8/67	Nitrogen mustard
8/67	Irradiation left cervical and left inguinal nodes, 2,500 rads
1/68	2,500 rads to left supraclavicular region
3/68-1/71	Chlorambucil; cyclophosphamide briefly in 1968
1/71-8/71	MOPP—six cycles
12/71	Irradiation of lumbar spine to 2,500 rads
1/72-4/73	MOPP—six cycles followed by maintenance every two months
7/74	Cyclophosphamide and prednisone
8/74	Bleomycin

MOPP = a regimen of nitrogen mustard, vincristine, procarbazine and prednisone

TABLE 2.—*Pertinent Hematological Data During the Patient's Final Year*

Date	*Hematocrit Percent*	*Platelets* $\times 10^3$	*Leukocyte Count* $\times 10^3$	*Blasts Percent*
5/ 1/74	36.5	226	7.6	0
7/ 3/74	26.3	75	2.1	0
10/ 2/74	13.0	45	1.2	0
10/22/75	16.0	40	0.9	0
10/29/74, Splenectomy				
10/31/74	32.4	45	5.1	"Rare"
11/13/74	27.4	130	14.5	8
11/27/74	26.8	230	23.5	19
12/11/74	24.8	350	33.1	43
12/18/74	19.8	259	40.0	47

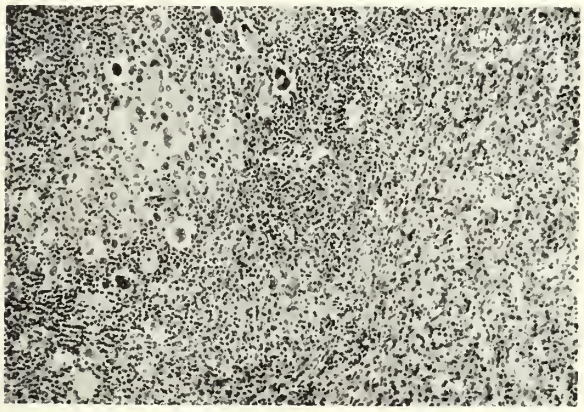

Figure 2.—Spleen, multinucleate cells consistent with Reed-Sternberg cells are seen. (Reduced from ×140)

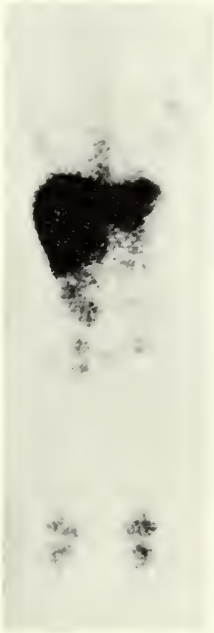

Figure 3.—^{111}Indium chloride total body scan showing diminished activity in the axial skeleton.

(Figure 4). Therefore, a bone marrow aspiration from the left proximal tibia was done on December 18, 1974. The peripheral blood smear (Figure 5) showed 47 percent blast forms, many of which had monocytoid features. No Auer rods were seen. The bone marrow smear was hypercellular with numerous myeloblasts consistent with the diagnosis of myelomonocytic leukemia (Figure 6). Cytogenetic studies of this marrow showed a karyotype of 45 XY 2P-/C- (Figure 7).

The patient's subsequent course progressively deteriorated; there was no evidence of response to therapy with doxorubicin hydrochloride (Adriamycin®), cytosine arabinoside, 6-thioguanine and prednisone. His course was complicated by septicemia, and the patient died on February 10, 1975.

On autopsy, widespread Hodgkin disease and leukemic infiltration of most visceral organs were noted. Review of the spleen slides did not show any leukemic infiltrates.

Discussion

Acute nonlymphocytic leukemia occurring in the course of Hodgkin disease has increasingly been noted in the last few years.[1-4] The most common characteristics of the patients reported include a prolonged period between the diagnosis of Hodgkin disease and the onset of leukemia; the mean duration is usually in excess of five years. Previous irradiation is another important

factor; apparently, its combination with chemotherapy enhances the risk for the development of leukemia. The response to therapy is very poor and the median survival after onset is one to three months. Our patient, therefore, is not exceptional in the duration of disease or previous therapy. The association of ionizing radiation with acute leukemia has been well documented in numerous studies of atomic bomb survivors[7-9] and population groups with significant exposure to diagnostic or industrial radiation.[10-17] On the other hand, Hutchison[18] reviewed a large series of women receiving radiotherapy for cervical cancer and found no increased incidence of leukemia. It is conceivable that Hodgkin disease is a preleukemic state and the longevity of these patients allowed this natural history to become apparent. This theory is interesting; however it is unlikely because in most long-term survivors leukemia never develops. Chemotherapy with melphalan has recently been associated with the development of acute nonlymphocytic leukemia in patients with multiple myeloma[19] and in women with ovarian carcinoma.[20] Another intriguing possibility is that the same biologic aberration leading to Hodgkin disease (that is, viral infection) may also be expressed clinically as acute myeloid leukemia.

Figure 4.—^{111}Indium chloride scan showing spot views of both knees; increased activity is shown.

Splenectomy for staging in Hodgkin disease has been established as an important component of patient management;[21] however, as a procedure for hypersplenism in this disease its use is not as well known. Rosenthal[22] first suggested in 1948 that splenectomy might be useful in leukopenic states to allow normalization of the granulocyte counts and further chemotherapy. Nies and Creger[23] later showed that patients with lymphoma and cytopenias secondary to hypersplenism respond quite favorably to splenectomy. Subsequent to splenectomy, chemotherapy in effective dosage could be safely resumed. Lowenbraun and co-workers[24] have shown that in cases of Hodgkin disease splenectomy was very useful in the management of their group of patients with cytopenias and hypersplenism. The resumption of chemotherapy at therapeutic dosage led to a high response rate. Although our patient had

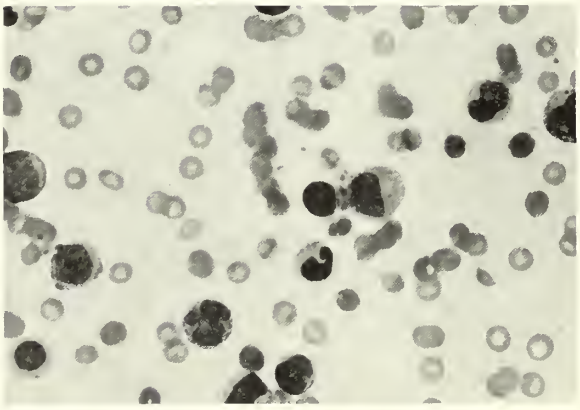

Figure 5.—Peripheral blood smear showing blast forms. (Reduced from ×630)

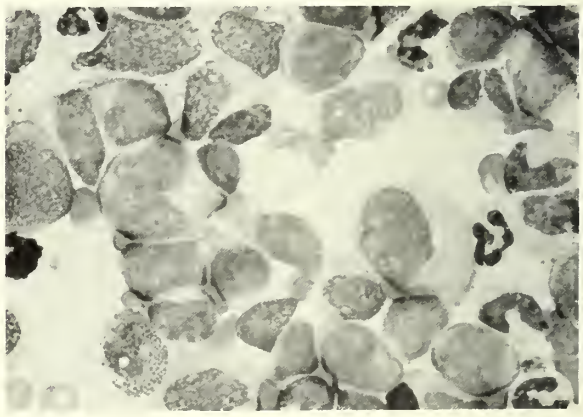

Figure 6.—Bone marrow aspirate showing numerous myeloblasts consistent with acute myelomonocytic leukemia. (Reduced from ×888)

significant marrow hypocellularity, we felt that hypersplenism was playing a significant role in the progressive pancytopenia and, therefore, a splenectomy was carried out. What role the splenectomy had in the appearance of the leukemia is unclear; however, there was no evidence for leukemia before splenectomy and the spleen was free of leukemic infiltration. The onset of overt leukemia in the immediate postoperative period has heretofore not been reported.

Cytogenetic evaluation of the bone marrow aspirate was done and deletion of a C-group chromosome and a portion of the short arms of chromosome 2 was noted. Chromosomal analyses in more than 20 patients in whom acute leukemia developed during the course of Hodgkin disease have been reported.[4,25,26] Abnormalities were universally present; hypodiploidy was frequent. Hodgkin disease, per se, has been shown to be associated with chromosomal aberrations; however, this has not been a consistent finding. We feel that the abnormalities noted in our patient were associated with the leukemic transformation. Chromosomal aberrations in acute myeloid leukemia are well described and the C-group appears to be a common site of abnormality.[27,28]

Finally, our patient presented a diagnostic problem. In the presence of blastic cells in the peripheral blood, neither iliac crest nor sternal marrow aspirations were diagnostic for leukemia. In fact, the iliac crest biopsy specimen was hypoplastic probably because of previous radiotherapy in adjacent areas. We therefore utilized ^{111}indium chloride to detect functioning erythropoietic marrow; a successful bone marrow aspiration specimen was obtained from the proximal tibia confirming the leukemic transformation. We are unaware that this scanning agent has been used successfully in this manner previously. ^{111}Indium chloride is a radionuclide that is very useful for imaging erythropoietic bone marrow.[5] Chemically ionic indium shares many properties with iron. When mixed with serum or injected at acid pH it readily binds to transferrin and therefore appears to compete with iron. Its bone marrow uptake is less complete than iron, resulting in a higher level of tissue background.[29] It is incorporated into erythroid precursors, probably in a similar manner as with iron. The transfer and incorporation allow one to image the functioning marrow with a nuclear medicine scanning device. Theoretically, radioisotopes of iron should be best for marrow imaging, but those available are not suitable for conventional imaging equipment. ^{99m}Technetium sulfur colloid has been used to image the reticuloendothelial component of the marrow, but it is only in the normal state that one can assume that the erythropoietic and reticuloendothelial compartments are identical. Therefore, at present ^{111}indium chloride is the only practical tracer available for erythropoietic imaging in a diseased state.[30] When the marrow is replaced by a myelophthisic process or suppressed by cytotoxic agents, or irradiation, no ^{111}indium

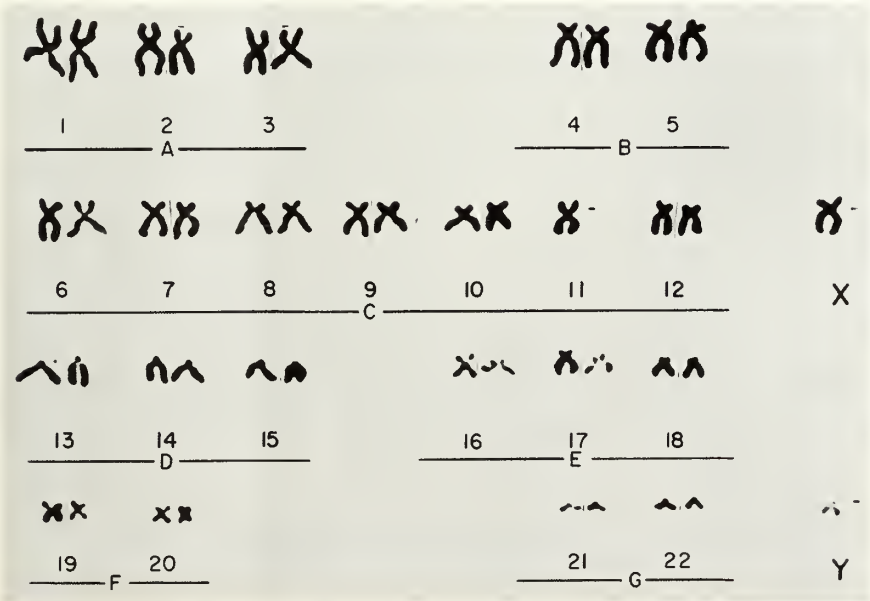

Figure 7.—Cytogenetic study showing a karyotype of 45 XY 2P-/C-. (2P-/C- is the nomenclature to indicate that a portion of the short arms of chromosone 2 and a C group chromosome is missing.)

chloride uptake occurs in the affected areas.[31] Consequently, its use in this case was ideal and the results obtained were gratifying.

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Infective Endocarditis Caused by Moraxella kingae

ANOUSH MIRIDJANIAN, MD
DON BERRETT, MA
San Diego

THE ROLE OF Moraxella kingae and closely related Gram-negative, pleomorphic bacilli (of the genera Neisseria, Bacteroides, Brucella, Hemophilus, Actinobacillus and Pasteurella) in human disease needs further definition. One previous case of endocarditis caused by Moraxella kingae or new species I has been reported in a 4-year-old child with a ventricular septal defect.[1] The following case documents infective endocarditis due to this organism in an adult.

Report of a Case

A 28-year-old man, a previously healthy lifeguard, had sudden onset of shaking chills, temperatures to 40°C (104°F), myalgias and headaches on June 23, 1976, three days after an abrasion on the right great toe. On June 27, a severe pain in the right femoral region lasted for several hours. On July 1, a half-hour episode of expressive aphasia during temperature elevation to 40°C led to hospital admission. A cardiac murmur was not noted on two previous physical examinations. The patient jogged and swam regularly and in competition without any apparent difficulty. He did not use drugs.

Abnormal findings on physical examination were: a flushed, acutely ill appearance; scleral injection and a hairline abrasion on the dorsum of the right great toe. Blood pressure was 130/80 mm of mercury, pulse 100 and regular, temperature 37°C (98.6°F). A right subconjunctival

From the Department of Internal Medicine and Bacteriology Laboratories, Southern California Permanente Medical Group and Kaiser Foundation Hospital, San Diego.

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Reprint requests to: A. Miridjanian, MD, 4647 Zion Avenue, San Diego, CA 92120.

hemorrhage and splinter hemorrhage on the right index finger appeared three days later. On the seventh hospital day, multiple petechial hemorrhages appeared on the patient's trunk and a grade I/IV blowing diastolic murmur was heard for the first time at the cardiac apex, left sternal border and right second intercostal space. There was intermittent tenderness in the left costovertebral angle, but no splenomegaly was noted. During this first week in the hospital, the patient had daily shaking chills with temperature elevations to 40.5°C (104.9°F).

On July 1, hemoglobin was 13.1 grams per dl, leukocyte count was 11,500 with 70 percent neutrophils, 4 percent bands and 15 percent monocytes. Sedimentation rate was 31 mm per hour. Urine sediment contained three leukocytes per high power field. Cultures of six blood specimens, drawn during the first 48 hours in the hospital, grew no organisms. Culture of a blood specimen drawn on the fifth hospital day was reported on the seventh hospital day as growing a pleomorphic Gram-negative organism. Subsequently cultures of seven blood specimens drawn after the fifth hospital day grew the same organism which was ultimately identified as Moraxella kingae. This identification was confirmed by the bacteriology laboratories of the Los Angeles County and State of California Departments of Health and the Center for Disease Control. Cultures of cerebrospinal fluid, bone marrow, urine, liver tissue and stool were negative. Several chest films, a gallium scan and an intravenous pyelogram showed no foci of infection. The latex agglutination test for rheumatoid factor was negative in the second and fourth weeks of illness. Six impacted molar teeth, including two extra third molars protruding into the maxillary sinuses, were extracted while the patient was receiving antibiotic therapy during the fifth week in hospital. No abscess was noted. Gingival tissues showed evidence of chronic inflammation.

The isolated organism proved to be very sensitive to penicillin (minimal inhibitory concentration 0.12 μg per ml, minimal bactericidal end point 0.24 μg per ml). The organism was also sensitive to ampicillin, chloramphenicol, cephalothin, erythromycin, kanamycin, tetracycline and methicillin. Excellent bactericidal levels were obtained with intravenous administration of penicillin G, 5 million units every six hours (1:128 four hours after the penicillin infusion). Because of the slow growth characteristic of this organism, however, the end point with this technique was not ideal.

The patient was maintained on 20 million units of penicillin daily for 28 days. He was afebrile after 72 hours of treatment with antibiotics. The intensity of the diastolic murmur did not change during treatment and congestive heart failure did not develop. Blood cultures were negative two and four weeks after therapy with penicillin was discontinued.

The patient remains well on follow-up examinations. No abnormality of the aortic or mitral valve leaflets is evident by echocardiography, although the patient clearly has the murmur of aortic regurgitation on auscultation and a slightly widened pulse pressure of 120/60.

Comment

The Center for Disease Control has 40 isolations from human specimens in its files on Moraxella kingae: 15 blood cultures; 9 throat cultures; 6 bone or joint aspirates, and 10 specimens from miscellaneous sites (personal communication, Dr. R. Weaver). The clinical disease associated with the samples is not on record for most specimens.

In man, the Moraxellae reside in mucous membranes of the eye, nasopharynx and genitourinary tract.[2] Moraxellae have been identified as causative agents of angular conjunctivitis since the late 19th century and more recently have been associated with septicemia,[3] purulent pericarditis,[4] septic arthritis,[5] meningitis,[6] endocarditis,[1,7] endophthalmitis[8] and corneal abscess.[9]

Moraxella kingae organisms are pleomorphic Gram-negative rods and sometimes produce pitting on blood agar. There is some question as to whether Moraxella kingae should really be classified as a member of the Moraxella group, primarily because M. kingae is saccharolytic, while other members of this group are nonsaccharolytic.[10]

It is possible that this patient's infection originated in the inflamed mucosal surfaces adjacent to the impacted molar teeth or in the toe abrasion that occurred three days before the onset of fever. The explanation for why a fastidious organism of low-grade pathogenicity might cause endocarditis on a normal valve is not apparent at this time. In the presence of known antecedent cardiac valvular disease or a heart murmur at the onset of illness, the pathogenic organism would not have been identified. Antibiotic therapy would have

been started, as is customary, after the initial blood cultures, without necessarily waiting for a positive culture report. We can only speculate that fastidious organisms, similar to Moraxella kingae, are pathogens in cases of culture negative endocarditis.

Summary

In a 28-year-old man without antecedent heart disease or a drug habit, infective endocarditis caused by Moraxella kingae led to aortic regurgitation. Intravenous administration of penicillin G (20 million units per day) for 28 days cured the infection. Six initial blood cultures were negative, delaying recognition of the pathogen.

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Aspirin Ingestion and Gastrointestinal Bleeding in Children

THE PROBLEM of gastrointestinal bleeding has changed somewhat in the past few years. If one looks at the standard textbooks on gastrointestinal bleeding in children, practically all of them indicate that in approximately 40 percent of the instances the cause is idiopathic or unknown. Those figures have changed nowadays, and the percentage is reduced at present to something like 3 percent or 4 percent. What happened to that great big segment? . . . There is a large group that used to come in bleeding; most of them had a respiratory infection and had been sick for three or four days and then they would come in with massive hematemesis and melena. The workup would be negative, even with an upper gastrointestinal series . . . sometimes with a laparotomy. When we go back into that group we find that most of them had received aspirin, at least one dose, during the time that they had the upper respiratory infection—and this is the culprit. We have found in recent years that aspirin can cause bleeding. I caution you to shy away from operating on a child who has had aspirin, because of upper gastrointestinal bleeding. It does not have to be a high aspirin level; it does not have to be a toxic level; it does not have to be a handful of aspirin; the child does not have to have eaten it, it could be given rectally—and it could still be responsible for the gastrointestinal bleeding. It is an idiosyncrasy that is accentuated by the respiratory infection in some way that we do not completely understand, but it is a cause of a high incidence of gastrointestinal bleeding, particularly in the pediatric age group.

—LESTER W. MARTIN, MD, *Cincinnati*

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

The Cost of Continuing Medical Education

To the Editor: In this era of required continuing medical education for physicians, continuing medical education has become big business. I believe no one would criticize continuing medical education for physicians. However, the avarice evident in the high cost of continuing medical education is unfortunate for those physicians whose gross income does not make tax deduction attractive. It is particularly disheartening that many of the exceptionally expensive postgraduate courses are sponsored by medical schools. Perhaps lower tuitions could be charged for physicians on fixed incomes.

ED SARGENT, MD
Student Health Center
Oregon State University
Corvallis, Oregon

Computers in Our Future

To the Editor: It is good to report that for those physicians and their spouses who attended the 1978 annual meeting of the Idaho Medical Association in Sun Valley, many fears and frustrations about the use of computers in medical practice have been dispelled, or at least lessened. The entire scientific program of the meeting was devoted to computers, and a team of physicians and technologists from the University of Wisconsin and Harvard put on a dazzling show, including on-the-spot demonstrations with an elaborate array of electronic equipment. As the professors spoke, the equipment bleeped and green and black electronic faces blinked. We physicians who came expecting to be bored, stayed on to listen and to learn, and to have many of our misconceptions swept away.

We were told that owing to the constant improvement in equipment, and with increasing experience, the errors computers make are being reduced to a bare minimum. In computerese, the "hardware" now available is of top quality and the "software" is dependable and adaptable. Upkeep is becoming less and less of a problem. As the volume of computerization increases, service is of higher quality and more generally available. It naturally follows that the cost of equipment will drop.

Several confusing technical details remain: We find that computers speak different languages. Will a universal language be adopted so that information can be instantly transmitted from, say, Boston to Los Angeles? Also, the concern about confidentiality lingers. Will stenographers on their coffee break be able to punch buttons to find out what patient has what disease? We were assured that information can be locked in, available only to authorized persons.

Up until now, when we were faced with a difficult diagnosis or a judgment call on the most appropriate form of treatment, we would "hit the books." It is now possible simply to "punch the buttons," and the machine will spew out the differential diagnosis or give the proper forms of treatment, in their order of preference.

Perhaps the most surprising (and disturbing) discovery was that a computer can take a better history than we physicians can. We must admit, if we reflect upon it, that patients often respond to our questions with less than total candor, or with answers they assume we want to hear. On the other hand, patients giving their history to a "box" that they themselves can manipulate, are found to be completely open and honest. Indeed, they seem to forget they are responding to a machine, and enter into a one-on-one conversation with the computer.

Finally, it was reassuring to be told, repeatedly, that the black boxes pose no threat to the white-coated doctor. Computers may be the almost perfect history taking machines, with an enormous capacity for digesting and storing data. They may, through their speed and accuracy, lighten our load in the office and at the hospital—even in the home. But even the most enthusiastic computer specialist quickly concedes that no machine can show concern, manifest love, radiate inner warmth or lay a gentle hand on a shoulder.

Let's face it, there are computers in our future.

But we will be their masters, they will be our helpmates. Our patient care will benefit—and we just might have a little more time for patient-caring.

E. R. W. FOX, MD
Special Editor for Idaho
Coeur d'Alene, Idaho

Removal of an Apical Aneurysm

TO THE EDITOR: In our report "Ventricular Tachycardia in a Young Adult With an Apical Aneurysm" (128:248, Mar 1978), we erroneously stated that removal of an apical aneurysm had not been "previously reported" in Chagas disease. To be correct, this statement should read "previously reported from the United States." We have since learned that a 46-year-old patient underwent aneurysmectomy for treatment of ventricular tachycardia in 1973 in Buenos Aires and this was reported by Castagnino and co-workers (*Medicina-Buenos Aires* 35:166, 1975). There may also have been others not reported in the literature who have undergone similar therapeutic measures.

W. ALLAN EDMISTON, MD
Los Angeles, California

Electroconvulsive Therapy

TO THE EDITOR: This refers to the article "Psychiatric Treatment—General Implications and Lessons from Recent Court Decisions" by Edward Rudin and Rick Zimmerman in the May 1978 issue (West J Med 128:459-466). The authors mentioned that "there were allegations that ECT [electroconvulsive therapy] was not accepted by the bulk of the psychiatric profession."

Research on this very question, by means of 4,000 questionnaires sent randomly to American Psychiatric Association (APA) members, showed that a majority do favor the use of ECT and are aware of the proper indications for ECT. This research was done by the APA Task Force on ECT. The report will be available in book form very soon.

ESTHER SOMERFELD, MD
Associate Clinical Professor Emeritus
Department of Psychiatry
University of Southern California
Los Angeles

JOACHIM HAENEL, MD
Formerly Associate Clinical Professor
Department of Psychiatry
Loma Linda University
Loma Linda, California

GEORGE WAYNE, MD
Clinical Professor
Department of Psychiatry, School of Medicine
University of California, Los Angeles
Medical Director, Edgemont Hospital
Los Angeles

Antinuclear Antibody Testing—A Correction

IN THE EPITOME "Antinuclear Antibody Testing" on page 56 of the July issue, the author's name was inadvertently omitted. This epitome was written by Edwin H. Krick, MD.

—EDITOR

Refer to: McHenry MM: Medicine in South India (Medicine in Perspective). West J Med 129:349-357, Oct 1978

Medicine in South India

MALCOLM M. McHENRY, MD, *Sacramento, California*

A three-month sabbatical allowed a superficial overview of Indian medical history and practice. As in Western nations, cost is a major determinant of health care delivery in India; poverty and fiscal shortages, however, deny care to many. The education of Indian physicians is similar to that in Western nations and a high level of clinical competence is seen. However, physician compensation is woefully low by Western standards. India possesses its own indigenous medical systems, purported to be the oldest in the world and predating Hippocrates by several millenia. Most Indians are cared for by native practitioners whose medical techniques are intricately related to the Hindu and Islamic religions. Many of their herbal medicines have been assimilated into contemporary Western practice. Diseases unknown to us except by textbooks are commonly seen and effectively treated. On the other hand, Western diseases such as coronary arteriosclerosis are not uncommon in a land of massive overpopulation and malnutrition. The humbling aspect of this experience is the realization that medical practice dating back several millenia can be made more modern and carried out competently by contemporary physicians. A Western physician working in India finds an unparalleled variety of disease in a totally different medical-religious environment allowing him to reorganize his priorities and to rediscover himself in the world within which he lives.

ADMITTEDLY, three months spent abroad in medical institutions in India hardly gives a physician wisdom or sufficient background to judge a country's system of health care delivery. Additionally, understanding of Indian medicine is complicated by many factors foreign to Westerners: religion, caste, astrology and, not in the least, economics. My comments, therefore, are impressions of Indian medical history and personal documentations of my own fascination with Indian medical care which is so different from that of our country.

From the Cardiopulmonary Diagnostic Center, Sutter Community Hospitals, and the Sutter Hospital's Medical Research Foundation, Sacramento, California.

Reprint requests to: Malcolm M. McHenry, MD, Cardiopulmonary Diagnostic Center, Sutter Memorial Hospital, 52nd and F Streets, Sacramento, CA 95819.

Health Care Delivery

The delivery of health care in India is similar to that in the West. Private physicians care for private patients. Those unable to afford private care can avail themselves of government hospital facilities. However, ever apparent is the financial limitation to scientific medical care. Indian physicians are frankly aware of the costs of health services. Expensive medicines such as the newer antibiotics, newer catecholamines and cancer chemotherapeutic drugs are seldom used. Laboratory tests are kept to a minimum.

The cost of a hospital bed in South India is about three dollars per day. Half the cost is for

nursing care and food which may be supplied by the family to reduce the hospital bill. This contribution by the family is a constant factor in aid to the ill. Families will care for the patient, cook his food, sleep beside him on the floor and tend to his needs in part because of a paucity of funds but in the main because of the devotion and care ingrained by centuries of charitable habit. In private hospital facilities in South India such common studies as x-ray films, electrocardiograms and blood counts must be paid for in cash before they are made. Drugs must be purchased before they are taken.

There is no health insurance in India. There is no prepaid medical care except that provided by large industries, large farms or plantations. Those people who do not have the wherewithal to afford the care which we consider standard, frequently leave hospitals to take their chances at home. No legal system protects a patient from poor care or forces hospitals or physicians to tend him. Malpractice suits are unknown on the Indian subcontinent.

Delivery of health care at specialized centers represents an additional problem. Referral hospitals in subspecialty areas draw from a large geographical area. In India, where there exist 15 major languages from Hindi, Urdu, Bengali and Maharati in the north to Tulugu, Tamil and Malayala in the south, few physicians can provide that essential part of any medical evaluation, the clinical history. Different Indian states act linguistically as different countries. For instance, in Tamil Nadu, the Sanskrit-Dravidian language contains 247 consonants, 12 vowels and a host of idioms which create a linguistic nightmare for western philologists. Consequently, in the referral medical community, English becomes the link language between physicians, nurses and paramedical personnel to interpret for patients.

Training

The training of an Indian physician begins at what we would consider the second year of high school or pre-university. Five and a half years transpire before he achieves his MBBS degree. He can then practice or can take one to two years of internship or house officership, as it is frequently called. To obtain the MD degree in medicine requires an additional three years (tantamount to residency), following which there is a certifying examination. If he wishes to subspecialize, he will then apply for and if accepted begin another two years of training for the DM or subspecialty degree.

Indian medical students do not study a core curriculum, as do students in most American medical schools, but study individual subjects in their basic science years. They are assigned to patient workup and hospital follow-up care as clinical clerks but do not prescribe or treat until they receive their graduate or MBBS degree. Competition for MD and DM degrees is keen at the leading medical centers, as would be expected. Those graduates working for advanced degrees impressed me as excellent clinicians. Many, however, on completion of training had difficulty in finding hospital positions. Well-trained Indian physicians find it difficult to work in the rural areas where indigenous practitioners abound.

Most allopathic or Western-oriented Indian physicians are trained in their own country. The capability of medical personnel I found at university centers was as good as in the West and physicians were possessed of considerable technical, teaching and practice skills.

In medical training programs in India a significant number of students are women. Many women physicians head clinical departments. With "arranged marriages" still common, men and women physicians are frequently matched. It was in a woman's medical college in Vellore that I principally worked (Figure 1 shows the states where I worked).

The Christian Medical College in Vellore was the vision and accomplished fact of a Cornell medical graduate of 1899, Dr. Ida Scudder, a member of a pioneer missionary family in India whose relatives still give their lives and talents and inspire others to do so. Her facility in Vellore in Tamil Nadu State, initially a hospital for women, grew into a nursing school, a medical college affiliated with the University of Madras, an eye hospital, and a world famous leprosarium at Karigiri where basic clinical and pathologic research in leprosy was followed by similarly unique reconstructive surgical procedures.

Indian physicians are poorly compensated by Western standards. In South India a full professor makes what is equivalent to less than $200 per month. Private practice is allowed to University physicians, but by contract all proceeds revert to the Medical College. Government-employed physicians, however, have the opportunity to practice privately using their homes as offices. Their total

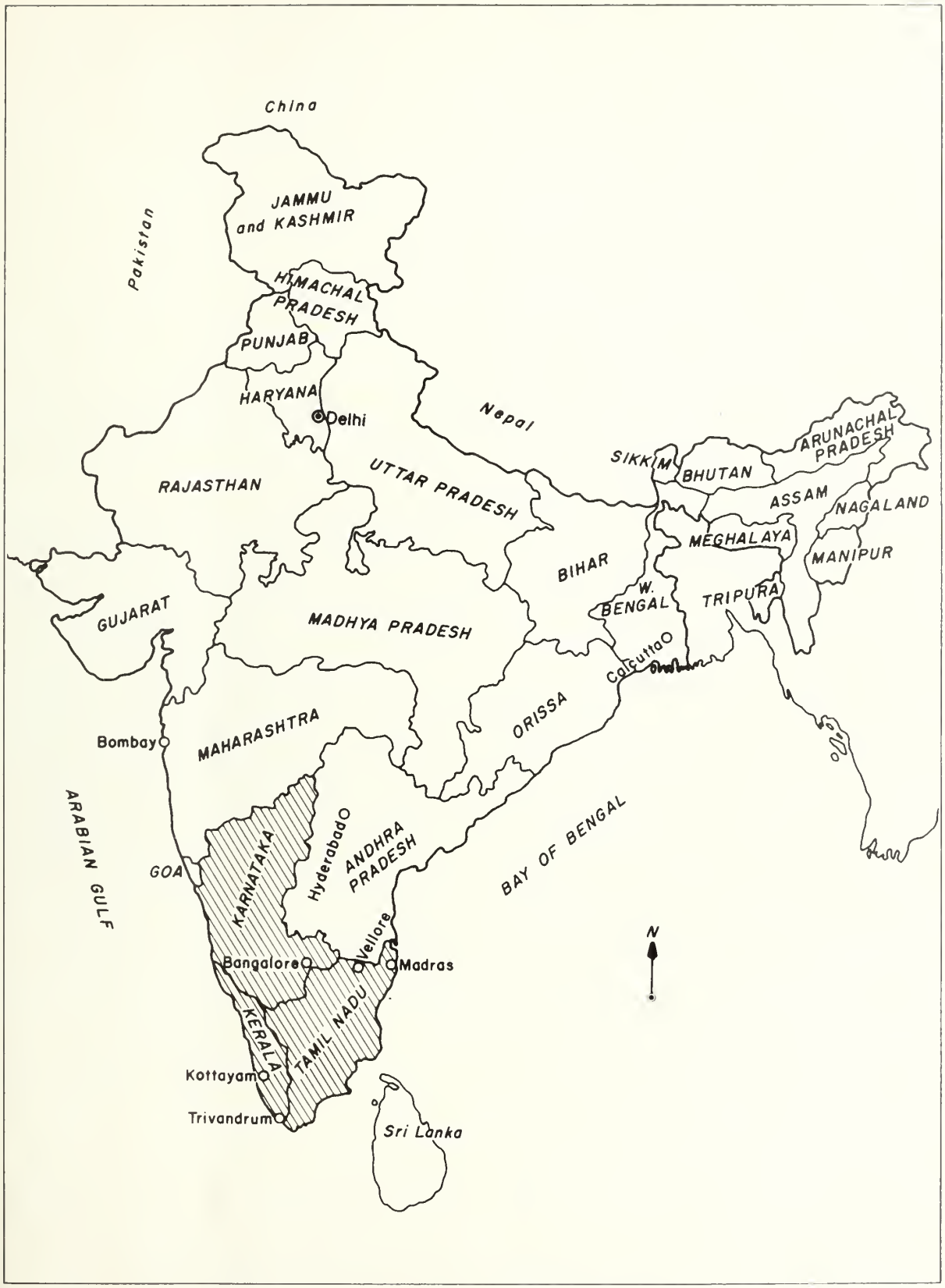

Figure 1.—The Indian subcontinent, smaller than the United States, but with 640 million people speaking 15 major languages, is depicted in this drawing. Shaded areas indicate states where the author worked.

income allows them to live well by Indian standards within their community but allows little latitude to travel. Transportation except by bus or railroad is expensive. Travel outside the country is prohibitively expensive and a limit of rupees brought out of the country is imposed by the government. A frequent lament of skilled Indian physicians was their inability to leave the country to travel abroad for training seminars or postgraduate specialization because the travel costs were high and it was difficult to find programs to accept them and pay their expenses. One cannot really criticize those young Indian doctors who find a way to leave their country, work at bare survival wages abroad but stay to make a living in an area where the standard of living is higher.

Indigenous Medical Systems

All medicine has its roots in ancient mythology and arose probably as an adjunct to magic. India is unique in possessing its own indigenous medical systems. The two principal schools are Ayurvedic and Unani-Tibb. Just as Varanasi (Benares, the holiest city of the Hindus) may be the oldest continuous actively functioning city in the world, native Indian medical systems lay proper claim to a pharmacopeia and a codified practice of the healing arts older than Greek or Egyptian ones. The earliest recorded physician (Imhotep, architect and advisor to the High Kingdom monarch, King Zozer) practiced in approximately 3150 BC. The Indian Vedas, verses and writings upon which Indian indigenous medicine is based, are said to predate this time.

The earliest recorded Indian texts, the Rgveda and Atharveda, were compiled about 3000 BC, but evidence suggests that the Ayurveda concepts preceded this time and were developd by the early builders of the Indus Valley civilization. Ayurvedic texts are called Samhitas and express the concept of Tridosa, the three bodily humors of force, fire and cold whose imbalance produces disease states. Ayurvedic medicine attempts to regulate this imbalance through changes in diet, climate, massage, hydrotherapy, herbs and metals such that proper health can be restored. Yet more than a healing art, Ayurveda is a total social system concerned with the prolongation of healthy life and prevention of disease and senility and only secondarily concerned with curing illnesses. It exists as a philosophy of living properly to sustain health within the confines of the Hindu faith.

Ayurvedic translated from Sanskrit means "life knowledge." Its written tradition can be traced only as far as 600 BC but its noncodified practice appears to predate its first writings by three millennia. Historians and antiquarians admit that India was the birthplace of medicine and surgery, if not also the origin of the earliest Greek philosophy. The medicine of the Arabs is attributed to Western migration of Vedic practitioners. Avicenna (Abu Ali al-Hussein ibn Abdallah ibn Sina), a distinguished Persian physician of the ninth century AD and composer of the revered medical *Canon* (Q'anun), in his writing quotes the Vedic physician Charaka. Hippocrates, the "father of medicine," whose treatises were compiled from the fourth century BC to the second century AD, borrowed much of his materia medica from the Hindus. The father of Indian medicine, Rishi Atreya, wrote in 1350 BC that "the beginning of the art of healing is as ancient as life itself."

Ayurvedic originates from a Veda or song of the healing art supposedly of divine origin and expostulated by Brahma, the first member of the Hindu triad. The first treatises in Ayurveda were written about 500 to 600 BC. Charaka "the internist" in the first century AD described treatments for most common infectious diseases and composed an encyclopedia of medicine still used in India. Bhava Misra (1550 AD) purportedly mentioned the proper circulation of the blood, 100 years before Harvey's treatise. Susrutha, a professor at the University of Benares, basically a surgeon, accurately described anatomic dissections in the fifth century AD and was concerned with personal hygiene and antisepsis in surgery. His knowledge of obstetrics, forceps deliveries and caesarian section was extensive. He mentioned the use of medicinal liquors to produce insensibility to pain. He emphasized diagnosis by palpation of the pulse, auscultation and analysis of urine. He described vaccination for infectious diseases and mentioned hypnotism for treatment of the sick. His description of a surgical operation is interesting. The surgeon first prays. He keeps his hair and beard trimmed short and his nails short and clean. His dress is clean, as is the surgical room, wherever it may be, and the operating area is cleansed and fumigated with "disinfecting vapors" before and after operation. For suture material Susrutha used strings of dried ants. His descriptions of reconstructive surgical procedures on the face and limbs may form the initial description of modern plastic surgery.

Ayurvedic roots exist in Hindu philosophy and are codified in Sanskrit treatises, especially those attributed to Susrutha and to Charaka. These Samhitas, works in medicine and surgery, passed down through hundreds of generations, were eventually put to paper about 600 BC and describe the eight-limbed science of longevity as practiced by the Vedic physicians. These limbs included medicine; surgery; ear, nose and throat disease; pediatrics; treatment of poisoning; illnesses inflicted by demons (mental disease); health maintenance, and aphrodisiacs restoring youth. Pulse reading is emphasized and fledgling Vedics study with experienced gurus or have the profession passed to them from studied relatives. Most Indians still resort to Ayurvedic treatment when in need, although the practice has been criticized many times as nonscientific, unprofessional and lacking in the successes of allopathic or Western medicine. The persistence of Ayurvedic practice reflects in great part the importance of the Hindu religion to the Indian population. Without this intermixture of treatment and religion, and the religious sensitivity of the Vedic practitioner, many Indians would feel alone and uncomfortable and probably would seek no medical care at all.

Schools combining indigenous practice with allopathic courses in anatomy, science and medical skills were introduced in the north of India in 1822, by order of the British Viceroy. However, Ayurvedic therapy, although possessed of an enormous pharmacopeia of useful but often unstandardized compounds, still is deficient in technical knowledge and skills. Training of Vedics still relies heavily on drills in Sanskrit grammar, philosophy, rote memorization of verses and production of age-old remedies of questionable modern value. In Tamil Nadu, a variant form of Ayurvedic, called Siddha, is based on texts on alchemy. Indigenous Indian medicine is not taught in allopathic medical colleges. However, Ayurvedics will frequently attend allopathic schools and eventually practice a combination of the two disciplines.

Many of the drug preparations advertised as curative contain a large number of herbs frequently mixed with clarified butter (ghee) and boiled or distilled into semiliquid paste for oral use or external application. However much one may doubt the system, Rauwolfia was an accepted Ayurvedic drug for centuries and legitimate cases of "cures" of hepatitis and arthritis and of drug amelioration of diabetes mellitus fascinate the allopathic physician and intrigue him to further study this carefully guarded pharmacopeia. Vedic practitioners are quick to refer patients with surgical disease, infectious disease and other maladies where they feel their knowledge and skill to be inadequate.

Unani-Tibb, an extension of ancient Greek medicine following the school of Avicenna, moved eastward from Persia to the Indian subcontinent along with the spread of Islamic religion and political influence. Its practitioners (hakims) speak Urdu and are located mostly in the north. Their first professional school was founded in south-central India in Hyderabad in 1890. Similarities exist in the Unani-Tibb and Ayurvedic systems in the study of religious treatises, the use of pharmacologic remedies traditionally handed down by father to son and lack of a large body of technical and scientific knowledge. In Bengal, in the northeast of India, Unani-Tibb hakims are frequently a caste in themselves, the families devoting themselves to this type of care for centuries in similarity to the Vedics who frequently are caste Brahmins and allow for no others to assimilate their knowledge.

An interesting and surprising aspect of the healing arts of Unani-Tibb hakims is the medicinal usage of precious and semiprecious gems. Ground diamonds, garnets, jasper, rubies and Kashmiri sapphires are mixed within different vehicles. Each stone has a specified use for a specific disease. Also, hakim practitioners reduce fractures and then cast the extremity in a green mucoid substance ground from the stem of the plant Cissus Quadrangularis, a botanical relative of the grape. The gummy substance stabilizes the fracture as would a cast. Cissus compounds also are used a poultices to reduce swelling in inflammatory diseases, especially in the parotid gland swelling of mumps.

A uniform similarity of the two systems (Ayurvedic and Unani-Tibb) is in economics (fee for service) and the cost to the patient is usually well within his means, being a few annas at most. Both Ayurvedic and hakim practitioners abound in the large rural areas of India while in the large cities, which account for only 20 percent of India's population, allopathic skills are more frequently sought.

For treatment of acute sinusitis in Madras I sought the aid of an Ayurvedic practitioner since antibiotics were not available. For 10 rupees ($1.20) I received six ounces of a pleasant smell-

ing mixture of ghee, saffron, vinegar and herbs, one of which was the pungent cardamom. One teaspoon twice a day was prescribed. I developed an aggressive nasal discharge which did in fact clear my sinuses and relieve my intense frontal headache, maxillary pain and fever but which also produced a rather distressing diarrhea. I was told on my return that it was written that one could not cleanse the nose without at the same time cleansing the bowels and was quoted a Sanskrit reference which I quickly forgot.

Diseases in India

Life in India is difficult. The average Indian life expectancy is said to be 47 years. The poverty level, into which 50 percent of the Indian population falls, is 96 rupees a month, about $12 per month or $244 per year. Wages are small and the population density is incredibly high. Accordingly diseases are much related to population and hygiene. In Tamil Nadu there exists perhaps the highest incidence of leprosy in the world, 2.3 per 1,000 population. Goiter is endemic because the monsoon rains do not allow for the retention of iodine in the soil or water and no iodination of salt has been implemented. High methionine levels in southwest India (Kerala) have been implicated in a variety of diseases such as calcareous pancreatic diabetes and primary hepatic tumors. In the rural areas of southwest India diet consists principally of tapioca, bananas and coconut and these have been implicated in an inordinate rate of premature coronary disease. The concept that lean muscular hard-working males are immune to coronary disease cannot be substantiated in India. Tropical eosinophilia manifest by asthma, cough and inflammatory changes shown on x-ray studies is assumed due to microfilaria and can be effectively treated with diethylcarbamazone.

The use from childhood of a cud of betel nut, tobacco and lime called "pan" is reflected in the high incidence of epidermoid carcinoma of the mouth and tongue. Pulmonary tuberculosis is said to affect 40 percent of the total Indian population and not infrequently presents with the clinical features of acute pericarditis or pericardial tamponade. Buerger disease producing gangrene of all four extremities is common. A typical operating schedule at a hospital in south India will list three thyroidectomies for goiter, three gastrectomies for peptic ulcers and three amputations for Buerger disease. The latter is felt to be related to the heavy smoking of bidi, a tobacco rolled in a leaf. Bidi production is a cottage industry sponsored by the government and the habit commonly in southern India will find a user smoking 50 to 60 of these small cigarettes a day.

Smallpox appears rare in India now but the facial scars on Indian adults attest to its former presence. (According to the World Health Organization and experts at the Center for Disease Control, no smallpox has been reported in India for about two years.) Rewards for information about active cases are posted on billboards. Cholera and typhoid present continued difficulties especially after natural disasters such as the November 1977 cyclone and tidal wave in Andra Pradesh where some 60,000 to 100,000 people died. With water comes malaria. However, with the birth rate in India of 57,000 per day with a 20 percent perinatal mortality, within three days, this loss was recouped.

However much one is impressed with these diseases, though, their frequency cannot be ascertained because no uniform reporting system and no public health system exist in India. It is unlikely that such will ever be possible because frequently no birth certificates are issued and because the way in which children are named does not allow one to clearly distinguish brother from sister or generation from generation. This is especially evident in the Christian population of southern India where children assume the Christian name of the grandfather with differing Indian surnames.

One of my principal reasons for traveling to India was to see and study the civilization that produced Mohenjo Daro, the Allore and Ajanta cave art, Khajaraho's sculpture, the Taj Mahal and Meenakshi temples, and where a flourishing trade with Greece and Rome existed in the centuries just before and after Christ. I also wanted the opportunity to view cardiology in India and to practice it in an area of the world unknown to me.

Cardiovascular disease in India is as much a problem as hygiene, infection, contaminated water and population explosion. In the Indian population the most common cardiac disorder is acute and chronic rheumatic heart disease. An estimated 20 percent of the rural population has significant valvular involvement. The severity of the disease at a young age is extraordinarily impressive. Patients with severe calcific mitral stenosis are not infrequently seen in their teens and surgical operation, be it commissurotomy or valve replacement, is quite frequently necessary before a

patient reaches the age of 20. Perhaps one of the reasons for the high incidence of rheumatic fever is the paucity of therapy for streptococcal disease. Even in those who have had rheumatic carditis, the recurrence rate is high because adherence to prophylactic antibiotic therapy is poor. Penicillin prophylaxis in India is recommended until the age of 45 because of the frequency of recurrence in adults.

Endomyocardial fibrosis, previously reported as endemic only in East Africa (Kenya and Uganda) is frequently seen in southern India. Obstruction to right ventricular outflow produces right heart failure and ascites which have to an extent been ameliorated by surgical bypass of the right atrium or superior vena cava to the pulmonary artery. Systemic hypertension is common in India and is surprisingly easily controlled by adrenergic blockers and thiazide drugs. Propranolol is now being chemically manufactured in Madras by government agreement with British chemical industries.

Most astonishing to the poorly-informed Westerner or Western cardiologist is the frequency of severe pulmonary vascular disease in India. The pulmonary vascular bed of the Indian population is intensively and tardively reactive. Severe pulmonary hypertension is seen frequently in congenital heart disease with an astonishingly high incidence of the Eisenmenger complex in children and young adults. Rheumatic carditis is endemic and invariably diagnosed clinically. These unfortunate children, as stated, go on in early life to severe mitral valve disease and equally severe pulmonary hypertension which is not completely reduced by surgical commissurotomy or mitral valve replacement. Primary pulmonary hypertension is common as is the Lutembacher syndrome of atrial septal defect with mitral stenosis with an added Asian component of pulmonary hypertension. Perhaps the most impressive indication of pulmonary vascular reactivity in India concerns those patients with coronary artery disease in whom myocardial infarction and subsequent left ventricular failure develop. Not infrequently, these persons are found clinically or by cardiac catheterization analysis to have systemic systolic pressures in the pulmonary artery.

Cardiac surgery in Asia is advanced but at the same time limited. There are only four or five major centers doing such work. The limitation of surgery is paralleled by other deficiencies. There are only three practicing pediatric cardiologists in the country. Cardiopulmonary bypass of over two hours carries a high risk of death from "pump lung." Any bypass pump procedure may be more expensive than most Indians can afford and prosthetic devices such as heart valves and pacemakers are totally outside the ability of patients to purchase. Coronary bypass operations have been carried out in areas of epidemic disease but few statistics as to patient selection, surgical results and long-term survival are available.

In Vellore more than 4,000 closed mitral commissurotomies have been successfully done. The professional cost of this service to a patient is approximately 900 rupees ($115). However, the cost of utilizing the pump oxygenator for implanting prosthetic heart valves may drive the cost of surgery to between 10,000 and 20,000 rupees ($1,250 to $2,500), and an artificial heart valve will require an additional expenditure of 4,800 rupees. The cost of hospital stays for cardiac catheterization ranges from 900 to 1,100 rupees. Cardiac pacemakers manufactured in Hong Kong are less expensive than in the West, yet still cost about 16,000 rupees ($2,000). Government hospitals have the same fiscal obstacles to purchase of prosthetic devices and pacemakers as private facilities.

Pharmacopeia

Allopathic cardiac medications in India are little different from the West with one exception: verapamil. This agent, a papaverine derivative, impressed me greatly. It is widely used in South Africa, Western Europe, New Zealand and Australia and presently is under investigation in this country. This compound which alters the "slow current" of calcium ingress to cells has been described as the "jet-age treatment of supraventricular tachycardia" without effect on cardiac cellular automaticity and with a negligible effect on myocardial contractility. The drug produces high grade antegrade and retrograde atrioventricular block. Supraventricular tachycardia can be reversed in less than five minutes following intravenous injection. On occasion, systemic hypotension due to peripheral vasodilation will occur. When quinidine became virtually unavailable in India in 1973 because of price and decreased supply, verapamil became the treatment of choice in supraventricular tachycardia. In rapid atrial fibrillation, ventricular rate slowing could occur within minutes without the inherent problems of digitalis intoxication. Verapamil is now

used throughout the subcontinent for chronic control of ventricular rate in atrial fibrillation, allowing low-dose digitalis maintenance. Its effect on reentrant tachycardias has been useful in terminating and preventing the occurrence of supraventricular tachycardia in the Wolff-Parkinson-White syndrome as long as the mechanism is not atrial flutter or fibrillation where preferential conduction down the anomalous bypass tract may be facilitated. Recent reports suggest also its effectiveness in controlling the coronary spasm of Prinzmetal variant angina.

Other drugs used in India and of interest to foreigners, yet not concerned with cardiovascular diseases, are thalidomide, rifampin and dapsone, all indicated in various forms of leprosy. Dapsone is the mainstay of therapy for mycobacterium leprae, replacing chalmoogra oil, and if taken early or consistently in chronic lepromatous or tubercular leprosy can be curative. Hemolytic anemia and chronic methemoglobinemia are accepted complications. Rifampin is an ancillary antileprosy agent of considerable effectiveness. The acute erythema nodosum leprae reaction occurring after initiation of leprosy therapy or occurring for reasons unknown as an acute arteritis, neuritis, nephritis or hepatitis can be effectively treated with oral administration of thalidomide. The agent which produced phocomelia in Europe exists as an effective agent in Asia, used only in men or postmenopausal women with the alternative agent in the female reproductive years being corticosteroids. Oddalum, a figwort similar to digitalis purpurea, the standard foxglove, grows abundantly in India. With food a real scarcity in rural areas, intoxication following the ingestion of this plant is common and patients frequently present with symptoms similar to digitalis overdose.

General Impressions

Many other isolated experiences struck me as significant in India. Acute appendicitis as we know it in the West is virtually unknown in India, as is carcinoma of the bowel (perhaps, as Burkitt has inferred, because of a high fiber diet). Birth defects such as kyphoscoliosis and untended club feet are common. So is poliomyelitis and persons with this disease frequently present as paralytic beggars in the large cities. Congenital and traumatically acquired cataracts are common as in some areas is trachoma. In Vellore and in other areas of India dedicated groups of physicians and nurses will mobilize an eye camp in rural areas. It is not uncommon to carry out 100 or more cataract extractions a day, a much more effective form of therapy than that used by inexperienced practitioners who characteristically poke out the lens with an unsterilized needle with ensuing panophthalmitis and blindness. The quality of care of these traveling medical suites is exemplary.

Reconstructive surgical procedures for leprosy are a triumph over a disease first documented in the Hebrew Bible. Hands and feet deformed by traumatic bone resorption and ulcerations due to loss of sensation and proprioception can be straightened into functional positions by muscle and tendon transplantation. Braces, uniquely devised shoes and electronic pressure sensors all are employed to rehabilitate those patients unfortunate enough to have missed curative drug therapy in early life. Neural paralysis of the orbicularis oculis muscle causes a failure of the blink reflex leading to corneal drying, ulceration and frequently secondary blindness. A uniquely simple if not brilliant surgical procedure now allows the restoration of blinking and lubrication of the cornea by attaching the orbicularis oculis muscle to the masseter. When the leper chews, he blinks and vision is saved.

Psychiatric problems are common in India. The incidence of schizophrenia is equivalent to that of the rest of the world. In India, however, with its age-old tradition and culture and its veneration of meditation, experience, visions and god-oriented forces, the subject seeing visions and hearing voices may be tacitly approved as a holy man and not as a psychotic. The psychiatric problems requiring therapy are not unlike those of Vienna in the 1890's and hysteria and conversion reactions are quite common.

Asian history does not comment on African invasion or migration although this is surely possible with the suspected prior land bridge between Africa and Asia and with the Mogul-Islam relocation into India in the 8th century. Whether such miscegenation is at fault or not, sickle-cell disease in dominant and recessive form exists in apparent caucasian (Aryan) populations of northeast India and in as many as one third of the primitive Veddoid hill tribes of southern India. The disease, even in its dominant expression, is considerably milder than in Africa. In the south of India where malaria may be frequent, heterozygotes for the sickle hemoglobin are not protected from the falciparum parasite as they are in Africa. Altered

immunity of a sort seems also to be an important factor in the development of leprosy; patients with active mycobacterial disease seem to have altered cellular immunity.

Indian medicine seems to mirror and adapt to the practices of the West. The latest studies in Western journals are used to enhance medical treatment. Indian publications are in the main quite good, clinically oriented and intended to teach practitioners how to deal in contemporary expertise with common problems. Research in India seems, however, to be directed towards opposite ends of a spectrum. At the All India Medical Institute in Delhi, I observed advanced tissue culture techniques, hemodynamic and electrophysiologic techniques in investigative cardiology as well as many other types of basic science investigation. However, in Vellore and at the Shri Chitra Tirunal Clinical Research Center in Trivandrum (Kerala), clinical research and teaching were emphasized. The latter institution is a combined project in clinical research in neurology and cardiology jointly sponsored by the Indian Central Government and by contributions from the family of the former Maharajah of Trivangore. Here there is an impressive program of medical-industrial research to produce artificial heart valves of durability but made of available Indian metal and textiles to overcome the prohibitive price of foreign-import prosthetic valves.

Afterthoughts

What is the value of travel to an area of the world that most Westerners consider backward, dirty and disadvantaged? First, one dissolves the myth that Western civilization is the model to which all should be molded. The sheer age of Indian cultural tradition and heritage is awesome when we consider as Americans that we have only recently celebrated our bicentennial. Indian civilization predates our society by thousands of years and offers alternatives to the vast and complicated civilization within which we live. This is not to say that India itself is not a complex country. Nowhere in the world is there a more staggering political and industrial inefficiency and bureaucratic chaos than in what has been called the world's largest democracy. Yet where else in the world today can you feel safe in teeming, crowded cities? Where else are people spiritually at peace with themselves, do not fear death and with so few material possessions live and die gracefully? Indians are basically a happy joyful race. India may be dirty but nowhere is there litter; every stick, paper, leaf or can is used for household functions. Second, in India a physician can practice medicine in a scientific fashion unbothered by the concerns of time pressures and emergencies, of unpleasant responsibilities, of legal adversaries, paper bureaucracy, and patients with imagined illnesses and petty complaints. Stress within the medical profession is at a minimum. Medicine in India is a true profession of problem solving, deduction and prescribing which formerly existed in the Western world. Third, India represents a refreshing aspect of medicine where the problems and their solutions are basically evident. However, to carry out this vision of medical care is complexly difficult because of age-old social biases, racial and caste hatreds, religious conflicts, fiscal shortages, crushing overpopulation and political obstacles. In these obstacles to health care the actual practice of medicine becomes complex and perhaps little different from that throughout the Western world.

I found Indian doctors, nurses, technicians, basic scientists and students no less a part of the 20th century than ourselves. With an overwhelming responsibility to care for more than 640 million patients with limited funds and equipment, they utilize their minds and their hands with little recourse to technical and laboratory aids, and they use their resources both frugally and scientifically. India is primitive by our standards but open to most scientific investigation. An American immunopathologist from Cornell University working in Trivandrum expressed it in the following way: "you can take frozen serum from this country to the United States and study basic disease mechanisms important to world health." Knowledge of Asian and Indian medicine is important not only for discovering disease mechanisms but for discovering yourself in the world in which you live.

Refer to: Shearn MA: Nails and systemic disease (Medical Information). West J Med 129:358-363, Oct 1978

Medical Information

Nails and Systemic Disease

MARTIN A. SHEARN, MD
Oakland, California

Important diagnostic clues may be provided by changes in the nails. Because nail findings are easily observable and yield valuable information, attention to these features is often rewarding. Some of the nail changes that may be observed in systemic disorders are reviewed.

MANY SYSTEMIC DISORDERS leave their mark on the nails and, therefore, provide physicians with valuable clues to diagnosis. In spite of this knowledge, there has been relatively little attention paid to the nails, which is surprising in view of the fact that they are among the most accessible parts of the body and can be viewed with the naked eye, requiring no sophisticated equipment. Although similar findings occur on the fingernails and the toenails, the traumatic effects of shoes and more frequent mycotic infections make toenails less valuable for diagnosis.

Some of the more distinctive changes in the fingernails that have been observed in systemic disease are herein reviewed. Local disorders resulting from trauma, tumor and infection are well described in dermatologic literature and are not included here.

Nail Growth and Aging

Nails grow from the nail matrix, which is located approximately 3 to 4 mm proximal to the cuticle. The matrix and the nail bed are supplied with blood through the paired digital arteries, which provide a rich capillary loop system with many arteriovenous anastomoses. Nails grow approximately 0.1 mm per day, with more rapid growth in adolescence and a slower rate with aging. The dominant thumbnail tends to grow faster than the nondominant nail, and disease may slow nail growth. Pregnancy and hyperthyroidism are associated with increased rates of growth; starvation and lactation, with slower growth.[1]

The most detailed study of nail growth was reported by Bean.[2-1] In a remarkable effort spanning three decades, he observed the gradual slowing of his nail growth. In his early 30's the thumbnail grew from the cuticle to the free edge in 117 days; in his 50's the nail grew the same distance in 137 days. At the completion of his study ten years later, 144 days were required for the same nail growth. Seasonal changes in nail growth rate were not observed.

With aging, nails become ridged, more opaque, greyish in color and less flexible (Figure 1).

Longitudinal ridging appears in the early middle years, increasing with age, and may be aggravated by trauma, rheumatoid arthritis and peripheral vascular disease, among other conditions.

Handedness

The thumbnail may provide a clue to dominant handedness (Figure 2), a feature that might be of value in predicting the outlook of a comatose patient with a neurologic deficit. The dominant thumbnail has a wider base and the angles formed

Figure 1.—Longitudinal ridging of nail in normal aging.

Dr. Shearn is Director of Medical Education, Kaiser-Permanente Medical Center, Oakland, and Clinical Professor of Medicine, University of California, San Francisco.

Submitted June 2, 1978.

Reprint requests to: Martin A. Shearn, MD, Kaiser-Permanente Medical Center, 280 W. MacArthur Blvd, Oakland, CA 94611.

by the base and the lateral aspects of the nail are more obtuse. When a trained observer judged handedness in a blind fashion (when fingernails were draped, and crossed or uncrossed according to a coin toss), handedness was identified correctly in the great majority of the subjects.[5]

Lunulae

The lunula or half-moon is present in most normal people. Lunulae are almost always found in the thumbnails, even when absent in the other nails. However, approximately 5 percent of presumably normal persons, usually older ones, do not have visible lunulae. A number of illnesses also may cause the loss of the lunulae: these include trauma to the terminal digit, multiple myeloma, scleroderma (Figure 3), bone tumors and hyperparathyroidism.

Figure 2.—Thumbs of left-handed person uncrossed. Note wider base and more obtuse angles at the corners of the dominant thumbnail.

Dystrophy

Dystrophy of the nails results from a variety of conditions—hereditary, congenital and acquired. Dystrophic nails are seen in persons who constantly traumatize their nails by biting or picking. Dystrophy may result from faulty manicuring. Such nails may present with irregular, transverse lines. Dystrophy of nails may also be secondary to dermatologic conditions which affect the terminal digits.

Punctate leukonychia, or small white spots on the nails resulting from incomplete keratinization of the nail plate, is found at some time in virtually all people and has no clinical importance.

The partial or complete absence of the nails that occurs in the nail-patella syndrome serves to alert one to the renal failure associated with this condition.

Mees Nail; Beau Nail

Mees nail (Figure 4) is characterized by a single, transverse, narrow whitish line that runs the width of the nail plate and is seen on multiple nails. The condition was originally described in arsenic poisoning but appears to be a legacy of remote, serious medical disorders, such as septicemia, dissection of the aorta, acute renal failure, sickle cell anemia in crisis and poisoning with heavy metals. The approximate number of days since the serious event occurred can be determined by measuring from the cuticle to the transverse line, adding 3 to 4 mm for that portion of the nail which is hidden between the matrix and the cuticle, then dividing by the estimated average daily nail growth of approximately 0.1 mm.

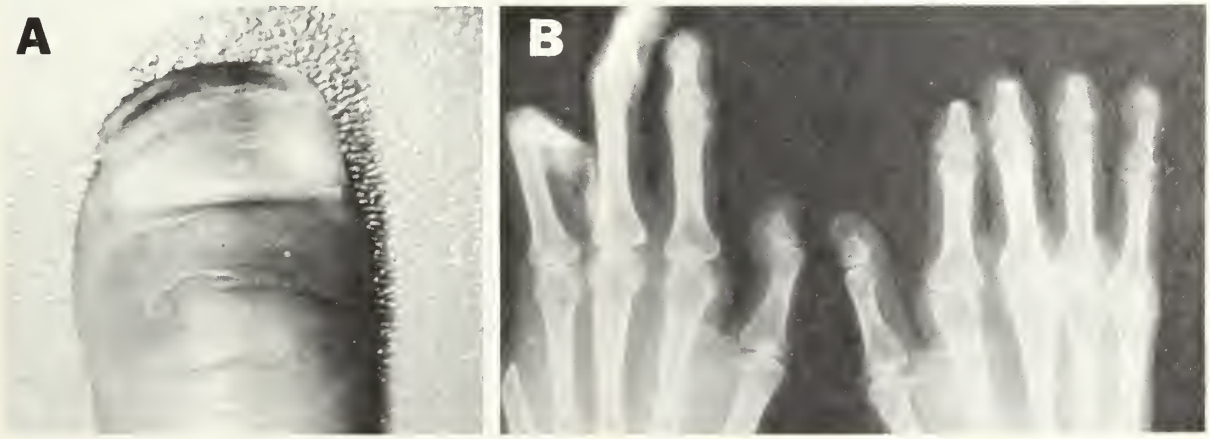

Figure 3.—**A,** Thumbnail of patient with scleroderma shows dystrophy and loss of lunula. **B.** Radiograph of hands of same patient shows bony abnormalities involving distal phalanges.

Beau nail, which displays a fault line appearance, is probably a more serious form of Mees nail that results from temporary arrest of growth at the nail matrix. In Beau nail, transverse deep depressions in the nail are seen, rather than the transverse white lines of Mees nail. The Beau line may indicate the same prior, serious medical events; the measurement is identical to that for Mees nail. Beau nail, like Mees nail, is seen at the cuticle edge approximately one month after the serious illness has occurred, as the average nail grows approximately 3 mm per month, the distance represented by the hidden area of nail growth.

Nail Pitting

In psoriasis, the nails are affected in approximately 25 percent to 50 percent of patients; in about 15 percent of these, permanent pitting occurs (Figure 5). In a patient with psoriasis whose cutaneous lesions have cleared, the presence of psoriatic arthritis is seldom considered, since such patients frequently forget to report a skin disease of the past, perceiving no connection of arthritis to that remote illness. However, the finding of pitted nails in an arthritic patient is of help in identifying psoriasis as a possible underlying cause of the articular disorder.

Rarely, nail pitting may be congenital, but the history of such nails since birth should avoid confusion with psoriatic nails.

Nails may occasionally be pitted as a result of neurotrophic conditions such as nerve damage. In such instances, the pits often clear with recovery.

The Reiter syndrome occasionally leads to pitting, but frequently the nails are surprisingly normal when the cutaneous lesions (keratodermia blennorrhagica) abate.

Clubbing

Clubbing of the nails has been of interest to physicians since its initial description by Hippocrates in empyema. It is known to occur in a variety of disparate conditions, only some of which have a common denominator. Many patients with clubbing such as those with cyanotic congenital heart disease have decreased arterial oxygen saturation; many others have some disturbance of pulmonary circulation. However, clubbing occurs in diseases as different as Crohn disease, ulcerative colitis, biliary cirrhosis, primary hypertrophic osteoarthropathy, cystic fibrosis and cancer of the esophagus. As with all diseases, the geographic distribution of illness should provide information, since the prevalence of a disease so often depends upon geography. For example, nail clubbing in northeastern Brazil is most often a manifestation of schistosomiasis of the lung which results in arteriovenous shunts decreasing arterial oxygen saturation.

Familial clubbing is unassociated with systemic disease and should offer no problem in differential diagnosis.

An objective assessment of the presence of clubbing can be obtained by measuring the ratio of the depth of the finger at the cuticle and also at the distal interphalangeal joint. The ratio is

Figure 4.—Mees nail. Note transverse white line on middle of nail plate.

Figure 5.—Pitting of nails in patient with psoriasis.

greater than one in digital clubbing and less than one in normal subjects.[6] Clubbed nails have been observed to manifest more rapid growth than normal nails.[1]

Renal Disease

Certain findings in the nail give valuable clues about the presence of renal disease. The nail-patella syndrome has already been mentioned. What has been termed the half-and-half nail (Figure 6), in which the proximal portion is white and the distal portion has a deep reddish color, was first noted by Bean and Clifton,[1] and subsequently studied by Lindsay.[7] Of the 25 patients whom Lindsay identified with the half-and-half nail, 24 had azotemia; the remaining patient had cirrhosis.

In nephrotic syndrome, the fingernails may also undergo a distinctive change, consisting of single or multiple transverse whitish bands seen in the nail bed. These bands described by Muercke[8] were found in patients whose serum albumin was less than 2.2 grams per dl. The bands were most prominent in patients with severe and prolonged hypoalbuminemia from any cause, although most of the patients were nephrotic. The banding regressed and disappeared when the serum albumin was raised toward normal.

Multiple splinter hemorrhages have been noted in patients undergoing hemodialysis. In one series, 20 percent of patients on dialysis manifested this finding.[9]

Figure 6.—Half-and-half nail (Lindsay nail) of renal failure.

Liver Disease

In chronic liver disorders, certain characteristic changes also appear in the nails. In cirrhosis of the liver, the nail may appear completely pale. The white nail has a high specificity for liver disease; less than 7 percent of patients without hepatic disease manifest this finding.[1]

The nail in liver disease may take on the appearance of a wide, pale, proximal portion and a narrow, deep-red distal portion (Figure 7). This finding, termed the three-quarter, one-quarter nail (Terry nail) is frequently seen in chronic hepatic cirrhosis but is not specific for liver disease; it may be observed in normal subjects and in patients with peripheral vascular disease, Raynaud phenomenon, systemic lupus erythematosus and also in other connective tissue disorders. The nails may give a clue to the presence of two chronic liver disorders that are potentially reversible: Wilson disease and hemochromatosis. Bluish lunulae have been observed in Wilson disease; in hemochromatosis, a blackish pigment, presumably melanin, appears on the nails as it does on the skin.

Pigmentation of the Nails

In addition to hemochromatosis, nails may undergo a variety of color changes from various drugs as well as from conditions that cause melanin or other pigments to be deposited. In

Figure 7.—Three-quarter, one-quarter nail of chronic liver disease shows distal band of deep color and larger, pale proximal area.

small cell carcinoma of the lung, adrenocorticotrophic hormone and melanin-stimulating hormone may be produced and may result in pigmentation of the nails as well as associated skin. Nail pigmentation may also be observed in Addison disease. With respect to drugs, tetracycline may produce a yellowish nail and chloroquine, a blue-black nail; adreamycin and cyclophosphamide[10] both have been reported to cause blackish nails. Argyria, which is a well-known cause of pigmentation of the gums, also results in a slate-grey color to the nails. Other causes of nail color change include industrial and cosmetic dyes, resorcin, pseudomonas infection, phenophthalein, and nicotine.

Blood Diseases

Chronic anemia produces a condition known as koilonychia, in which the nail becomes spoon-shaped. This condition is quite uncommon in developed countries but is seen with relative frequency in areas where chronic anemia, secondary to parasitic disease, is widespread. Hemorrhages under the nail plate are found in leukemic patients and in those with bleeding diatheses.

Miscellaneous Conditions

The yellow nail, which presents as a thick, opaque slow-growing nail, is seen in lymphatic blockage. Onycholysis, in which the distal portion of the nail is pulled away from the bed, is a sign of hyperthyroidism (Plummer nails) and also is found in hypothyroidism, in traumatic conditions, fungus disease, impaired circulation and psoriasis.

Connective Tissue Disorders

The diagnostic value of splinter hemorrhages (Figure 8) was mitigated following a report in which about 10 percent of hospital inpatients had this finding;[11] however, patients in hospital frequently harbor infections, vasculitis, renal failure and other diseases in which immune complexes are found. Immune complexes are thought to participate in the production of the subungual hemorrhages. An occasional splinter hemorrhage is of no diagnostic value and is often the result of trauma; however, multiple splinter hemorrhages, especially when trauma can be eliminated, increase their diagnostic value. Splinter hemorrhages in profuse numbers are found frequently in systemic lupus erythematosus, renal disease, rheumatoid arthritis, mixed connective tissue disease, vasculitic syndromes, bacterial endocarditis and trichinosis. They have also been observed in eosinophilic polymyositis.[12] These lesions, which involve the spirally wound capillaries, are deep in the hyponychia and give a positive benzidine test.[13]

Dermatomyositis causes an erythema of the distal nail folds (Figure 9). This condition is associated with hyperkeratotic thickening and roughening of the cuticles.[14]

Figure 8.—Splinter hemorrhages in patient with vasculitis.

Figure 9.—Erythema of nail folds in patient with dermatomyositis.

The capillaries in the skin proximal to the cuticle can be viewed by the naked eye but are seen more clearly with a magnifying lens and a drop of oil. Giant capillary loops adjacent to areas with no capillaries are common to dermatomyositis and scleroderma and are rarely observed in other connective tissue disorders. The finding of giant capillary loops in a patient with Raynaud phenomenon is evidence that the condition is not innocent and that there may be an associated collagen disease.[15] These large capillary loops have also been observed in patients who develop a scleroderma-like disorder when exposed to polyvinyl chloride.[16] In systemic lupus erythematosus and rheumatoid arthritis, one may see an increased size of nail fold capillaries which have the appearance of a picket fence, but giant loops are rarely seen. In various disorders associated with arteritis, small infarcts about the nail folds occur. In such instances, an arteriogram of the hand will often show changes that are typical of vasculitis.

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Advantage of 'Pencil-Point' Needles in Reducing Postspinal Headaches

We are limited, or should be limited as much as possible, to 25-gauge spinal needles (when doing subarachnoid blocks) in order to avoid postpuncture headaches. It is a more difficult technique than it would be on a medical ward where large size needles such as an 18-gauge or a 20-gauge needle are frequently used. If one wishes, instead of using a 25-gauge spinal needle, without increasing the risks of postpuncture headaches, one can use pencil-point type needles such as the Whitacre needle—which is commercially available. The advantage of the Whitacre needle is that it has the rigidity of a 22-gauge needle, but separates the fibers rather than cuts them and hence this diminishes the incidence of postpuncture headaches to that of the level of a 25-gauge spinal needle.

—WILLIAM GOTTSCHALK, MD, *Chicago*

Extracted from *Audio-Digest Obstetrics and Gynecology*, Volume 25, Number 9, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1577 E. Chevy Chase Drive, Glendale, CA 91206.

ARTICLES TO READ IN OTHER JOURNALS

EDITOR'S NOTE: *Members of the Editorial Board on occasion call attention to articles that they consider to be important in other journals. The editors believe that these titles together with a brief assessment of the articles are worth publishing for the information of our readers.*

Editorial: Evaluation of Computed Tomography: Achievement and Challenge
Fineberg HV
American Journal of Roentgenology
131:1-4, Jul 1978

Because technological obsolescence of a $600,000 or $700,000 computed tomography (CT) *unit may antedate its depreciable life, it symbolizes the dilemma of health technology. Trying to evaluate* CT *is trying to hit a moving target that is also changing shape.*

Clinical Efficacy of Computed Body Tomography
Wittenberg J, Fineberg HV, Black EB, et al
American Journal of Roentgenology
131:5-14, Jul 1978

CT *contributed to a decision not to carry out contemplated surgical procedures in 21 percent of patients. It improved diagnostic understanding in 41 percent, reassured physicians about previously planned therapy in 43 percent, contributed to a change in therapy in 17 percent and improved precision of previously planned therapy in 10 percent.*

Observations on the Medical Efficacy of Computed Tomography of the Chest and Abdomen
Robbins AH, Pugatch RD, Gerzof SG, et al
American Journal of Roentgenology
131:15-19, Jul 1978

Out of 687 CT *studies of chest and abdomen,* CT *alone obviated 16 thoracotomies and 18 laparotomies.*

Cranial Computed Tomography in Diagnosis and Management of Acute Head Trauma
Zimmerman RA, Bilaniuk LT, Gennarelli T, et al
American Journal of Roentgenology
131:27-34, Jul 1978

The CT *series showed an 84 percent reduction in arteriography, 58 percent reduction in surgical intervention and 24 percent reduction in skull radiography. Mortality for intracerebral, subdural and epidural hematomas was lower than for the series immediately preceding* CT.

Computed Tomography in Patients With Cerebrovascular Disease: Impact of a New Technology on Patient Care
Larson EB, Omenn GS, Loop JW
American Journal of Roentgenology
131:35-40, Jul 1978

CT *resulted in little demonstrable improvement in the care of patients with cerebrovascular disease but did increase the cost of the evaluation.* CT *improved care but did not increase cost for patients with brain tumors.*

See related editorial **"Computed Tomography: Its Efficacy and Cost"** in this issue.

Impact of Computed Tomography on the Care of Patients With Suspected Hydrocephalus
Larson EB, Omenn GS, Magno J
American Journal of Roentgenology
131:41-44, Jul 1978

CT *reduced cost of neurodiagnostic workup by 22 percent. It reduced the need for pneumoencephalography.*

Efficacy of Computed Tomography of the Head in Changing Patient Care and Health Costs: A Retrospective Study
Bahr AL, Hodges FJ
American Journal of Roentgenology
131:45-49, Jul 1978

Costs and hospital stays were reduced in comparable patient groups, and especially in those with extracerebral collections and tumors.

Comparison of Computed and Conventional Whole Lung Tomography in Detecting Pulmonary Nodules: A Prospective Radiologic-Pathologic Study
Schanner EG, Chang AE, Doppman JL, et al
American Journal of Roentgenology
131:51-54, Jul 1978

CT *detected more nodules than conventional tomography in 48 percent of cases. However, 60 percent of these proved to be benign granulomas or nodes.*

Computed Tomography of Musculoskeletal Disorders
Wilson JS, Korobkin M, Genant HK, et al
American Journal of Roentgenology
131:55-61, Jul 1978

CT *provided unique information leading to a correct diagnosis in 45 percent of cases.*

Efficacy of CT-Assisted Two-Dimensional Treatment Planning: Analysis of 45 Patients
Ragan DP, Perez CA
American Journal of Roentgenology
131:75-79, Jul 1978

CT *afforded measurable improvement in treatment planning—greatest in brain, lung and retroperitoneum.*

Computed Tomography: Cost and Efficacy Implications
Abrams HL, McNeil BJ
American Journal of Roentgenology
131:81-87, Jul 1978

This thoughtful and factual discussion includes costs of equipment and of maintenance, utilization and obsolescence. Distribution of CT *units and the impact of Certificate of Need regulations are considered, as are measures of effectiveness.*

DISCIPLINES: All of these articles are relevant for all physicians, administrators and even bureaucrats.

READABILITY: Good to excellent throughout.

—ROBERT B. ENGLE, MD
Orange, California

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BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

ADOPTING THE PROBLEM-ORIENTED MEDICAL RECORD IN NURSING HOMES—A Do-It-Yourself Manual—Howard F. Corbus, MD, Assistant Dean for Community Hospital Affairs, University of California, San Francisco, Fresno; Director of Nuclear Medicine, St. Agnes Hospital, Fresno, California; and Laura L. Swanson, RN, Director of Nursing, San Joaquin Gardens, Fresno. Contemporary Publishing Inc., 12 Lakeside Park, Wakefield, MA (01880), 1978. 108 pages, $5.95 (softbound).

This booklet is written in precise language and short sentences. No jargon is used. The directions are brief, but complete, and can be easily followed. If a nursing home is interested in adopting problem-oriented medical records, this booklet could be most valuable. If the booklet has any fault, it lies in the impression of simplicity imparted to a very challenging project. The authors point out that "total commitment to and enthusiasm for this undertaking" is necessary. And so it appears. There is a lot of hard work and especially teamwork called for in the booklet and mutiple copies would have to be made available to the various staff members to make the switch over from traditional records to problem-oriented records work. No team thrives unless each member knows exactly what is expected of him and why it is important, and either possesses or is helped to develop the skills necessary to carry out his assignment. A good plan—one that all members of the team helped design—is fundamental. This booklet presents a good plan.

The authors, I think, enjoyed writing it, and nurses, I think, will enjoy using it. But nurses of another era past, who do not recognize the value of good records and are reluctant to seek new values, need not apply.

WALTER A. ROHLFING, MD
Fresno, California
Chairman, Long-Term Care Review Committee
California Medical Association

• • •

CURRENT DIAGNOSIS 5—Edited by Howard F. Conn, MD, and Rex B. Conn, MD. W. B. Saunders Company, West Washington Square, Philadelphia (19105), 1977. 1272 pages, with 104 illustrations, $34.00.

Current Diagnosis is half a book. Along with *Current Therapy* it would make up a whole book.

Current Diagnosis is another multiauthor textbook of medicine. The typeface in the body of the book is clear and easy to read. The type in the index is small and faint and hard to read. There are few pictures and the reproductions of x-ray films are poor. Echograms and nuclear scans showing abnormalities are not given with normal ones for comparison. There are no references or directions for further reading.

The eight-page table of contents ends with a category titled "Diseases of Unknown Cause" in which four diseases are listed (sarcoidosis, Sjögren, Reiter and myasthenia gravis). Inasmuch as most of the diseases in the other eight pages are of unknown cause the editors might better have titled this last category "We Didn't Know Where to Put These." Even editors become exhausted.

To tie together the confusion of 300 authors the editors note that they have "incorporated numerous cross-references and an extensive index." To test this I looked up deep vein thrombophlebitis of the leg. Under the heading "thrombophlebitis" the index gave three references: "as transfusion reaction," "postpartum" and "superficial." I then looked in these places and found nothing of the thrombophlebitis I had in mind. Fortunately, the last, "superficial," was in an article which began two pages previously and was titled "Peripheral Venous Disease." That article covered deep vein thrombophlebitis of the leg very well—along with the most current methods of diagnosis. My finding the information, however, was purely by chance, with no credit to the index or cross-references.

It would be ridiculous to think that 300 experts would fail to provide plenty of useful information. They do provide plenty, but in trying to serve two masters—students and practitioners—they sometimes serve one at the expense of the other. For example, the first three articles are "Fever of Unknown Origin," "The Acute Infectious Disease Syndrome" and "Chronic Cough." I do not believe I need to be reminded in these articles that the following, respectively, are essential: "A detailed history and physical examination with careful attention paid to small details," "a careful history, a meticulous physical examination, and appropriate laboratory procedures" and "As with any diagnostic problem, a detailed history and physical examination are essential." No wonder the book is so heavy.

The philosophy of the book is valid—that advances in diagnostic knowledge deserve frequent publication in textbook form just as advances in therapy do. However, the authors so assiduously avoid discussion of therapy that many have missed the interplay of therapy and diagnosis which so often constitutes the clinical situation.

I compared *Current Diagnosis* with the recently published textbook of medicine I have in my office. I found *Current Diagnosis* more up to date in very recent diagnostic concepts and procedures. However, because my present textbook includes diagnosis *and* treatment in the same article, it was easier to use.

DAVID LEIGH RODGERS, MD
Associate Clinical Professor of Medicine
University of California, San Francisco
Associate in Medicine
Stanford University School of Medicine

• • •

ALVAREZ ON ALVAREZ—Walter Clement Alvarez, MD. Strawberry Hill Press, 616 - 44th Avenue, San Francisco (94121), 1977. 160 pages, $5.95 (Paperback). (Distributed by Stackpole Books, Cameron & Kelker Sts., Harrisburg, PA 17105.)

This delightful second autobiography of one of America's best known physicians, portrays a life of over 90 years devoted to medicine and people. Walter Alvarez's love of his family, of medicine and of people runs through the pages like a wide golden thread. He came by these naturally with a father, Spanish by birth and a physician, and a mother of German descent strongly devoted to her family. In his early days in medicine, practice was his greatest interest but with an insatiable curiosity which was always asking him "why," he moved gradually more and more towards research and investigation particularly in the function of the gastrointestinal tract which became his major first interest. From this arose the inevitable struggle between the economic needs of his family and practice and the love of investigation. As he gained increasing stature in the profession, indeed its very height, as a member of all the prestigious societies in internal medicine, the pressures became so great that in 1926 he joined the staff of the Mayo Clinic in hopes of carrying on with his investigation and practice

in a rational and productive relationship. Frustrated in part by limitations in capacities to carry this out effectively, he more and more turned his tremendous energies to clinical consideration of patients with functional disorders of the digestive tract, constitutional inadequacies, tensions, anxieties, worries, fears and fatigue, and related disturbances. Recognizing the close relationship between these conditions and disturbed functions of the GI tract, he soon became a master in recognizing and dealing with patients who had them. Because of this, he greatly enhanced his ability to communicate with them effectively, and, equally important, to communicate very effectively with members of the medical profession and with laymen. He wrote extensively, articles for medical journals and books, and quickly became the best known and most widely sought-after speaker at medical meetings in this country.

The last third of his life, after he retired from the Mayo Clinic at 65, was devoted largely to communication—writing articles, and books for physicians and laymen on the subjects of nervous indigestion, neuroses, and the digestive tract. His very popular column in daily newspapers all over the country for years carried great weight because of his sound, scientific base and his great talents in writing simply, clearly and in an interesting fashion, drawing upon his enormous experience in medicine.

Walter Alvarez knew people, he understood their needs, he explained complicated medical things to them in a simple way often with embellishments of his own or a patient's experience. What he wrote rings true to the reader—it is real.

Dr. Alvarez was well past 90 when he died this year. He lived quietly but still enjoying old friends, full of energy, writing, always thinking of the new. He looked back in this autobiography on a life unique in this century which for him was enmeshed with a happy family, medical science, clinical investigation, outstanding ability to communicate entertainingly what he experienced and knew with his family and countless friends, readers and admirers. In this book they will be reminded of a very important and happy relationship.

DWIGHT L. WILBUR, MD
San Francisco

* * *

CARDIAC EMERGENCIES—Edited by Dean T. Mason, MD, Professor of Medicine; Professor of Physiology; Chief, Cardiovascular Medicine, University of California, Davis, School of Medicine, Sacramento Medical Center, Davis and Sacramento; President, American College of Cardiology; with 34 contributors. The Williams & Wilkins Company, 428 E. Preston St., Baltimore (21202), 1978 408 pages, $29.50.

Recognizing that cardiovascular disease is the major cause of death in the United States, Dr. Dean Mason has compiled current information on the primary cardiovascular emergencies encountered today by practicing physicians. The proper techniques for cardiopulmonary resuscitation and the therapy of acute heart block are carefully described and should be thoroughly known by every physician who actively treats patients. The signs and the symptoms of acute myocardial infarction are differentiated from dissecting thoracic aneurysm, pulmonary embolism and thoracic chest wall pain. The treatment of congestive heart failure and cardiogenic shock utilizing pharmacologic therapy and, when necessary, mechanical cardiac assist devices, is succinctly reported. The medical treatment of preinfarction angina described by the Stanford group provides an interesting contrast to the aggressive surgical approach of the University of California, Davis, group. Dr. Henry De Mots summarizes the current knowledge of acute pulmonary edema which commonly follows significant elevation of pulmonary capillary pressure but which may also occur following fluid overload, pulmonary embolism, pulmonary aspiration, narcotic overdosage and diffuse capillary leakage.

Cardiac, vasodepressor and orthostatic syncope are differentiated by Drs. Cohn and Calanchini, primarily on the basis of the history of the event, the premonitory symptoms, the postition of the individual patient and the postsyncopal state. The major tachyrhythmias and the complications of temporary and permanent transvenous pacemakers are described by Dr. Mason's group. Guidelines are given for accurate detection and prompt management.

Cardiac Emergencies is written by recognized authorities in cardiovascular medicine—many of whom practice in the West. The book is not intended to be an encylopedic reference source but rather it provides current information on the primary cardiovascular catastrophes. Recent references from the medical literature are provided for physicians who seek more complete information. The essential elements of each chapter are summarized by Dr. Mason in his discussion on the present progress in cardiovascular emergencies. Numerous tables and figures are provided throughout the book in order to emphasize important information. This text will be useful to critical care nurses, medical students, physicians in training and practicing physicians.

ROBERT J. HENNING, MD
Associate Professor of Medicine
University of Southern California
Los Angeles

* * *

AID™—The Antibiotics Indications Device—Developed by Excerpta Medica Services, Inc., Editorial Consultant Committee (Chairman: Maxwell Finland, MD, Professor of Medicine, Harvard University). Excerpta Medica Services, Inc., PO Box 3085, Princeton, NJ (08540), 1978. 28-page booklet, plus device in back-cover pocket: 3 or less, $11.95 each; 4 to 10, $10.75 each; 11 to 25, $10.25 each; quantity discount prices upon request.

Virtually every physician prescribes antimicrobial drugs daily. The constant proliferation of drugs and the rapid changes in the behavior of microorganisms toward them makes it desirable that some convenient aid for the selection of drugs be available. Many such reference sources appear every year. Perhaps the most widely used, concise, reliable and up-to-date is the "Handbook of Antimicrobial Therapy" published every year by the "Medical Letter."

The present *AID* consists of a 28-page booklet which lists five pages of "directions" for its use, nine pages of drug choices in common and "less frequent" infections, a table of common toxic effects attributable to antimicrobials, four pages of brand names (12 brands of ampicillin, 12 brands of penicillin V, 7 brands of tetracycline HCl and so on) and three pages of common drug dosages, plus a few pages of general advice. The same choice of drug and dose is also provided in the pièce de résistance, a plastic slide-rule-like gimmick. Bibliographic references date from 1969 to 1976 for this 1978 publication of *AID*—of doubtful relevance in an area where changes must occur every year.

$11.95 seems a high price to pay for the "gimmick" aspect of this *AID*, as the same recommendations are available in many other publications that appear yearly and cost very much less. Also, the plastic "slide-rule" threatened to tear my pocket when I attempted to carry it on the ward.

ERNEST JAWETZ, MD, PhD
Professor of Microbiology and Medicine
University of California, San Francisco

in memoriam

Arosemena, Roberto D., Long Beach. Died July 11, 1978 in Lakewood of heart disease, aged 56. Graduate of the University of Panama Medical School, 1957. Licensed in California in 1958. Dr. Arosemena was a member of the Los Angeles County Medical Association.

Cooke, Harry H., San Clemente. Died December 23, 1977 of cancer of the pancreas, aged 80. Graduate of the University of Minnesota Medical School, Minneapolis, 1924. Licensed in California in 1944. Dr. Cooke was a member of the Los Angeles County Medical Association.

Hayashi, Donald T., San Francisco. Died August 12, 1978 in San Francisco, aged 49. Graduate of the University of Rochester School of Medicine and Dentistry, 1954. Licensed in California in 1956. Dr. Hayashi was a member of the San Francisco Medical Society.

Holleran, George C., Brawley. Died July 28, 1978 in San Diego, aged 75. Graduate of the Creighton University School of Medicine, Omaha, 1928. Licensed in California in 1929. Dr. Holleran was a retired member of the Imperial County Medical Society.

Kirk, Marvin E., Oakland. Died July 10, 1978, aged 81. Graduate of Jefferson Medical College of Thomas Jefferson University, Philadelphia, 1926. Licensed in California in 1926. Dr. Kirk was a retired member of the Alameda-Contra Costa Medical Association.

Lambert, Harold W., Berkeley. Died July 26, 1978, aged 73. Graduate of the University of California Medical School, Berkeley-San Francisco, 1931. Licensed in California in 1931. Dr. Lambert was a retired member of the Alameda-Contra Costa Medical Association.

Lamont, Herbert A., Long Beach. Died June 2, 1978 of carcinomatosis, aged 78. Graduate of Northwestern University Medical School, Chicago, 1925. Licensed in California in 1925. Dr. Lamont was a retired member of the Los Angeles County Medical Association.

MacKinnon, Donald S., Los Angeles. Died August 2, 1978, aged 73. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1931. Licensed in California in 1931. Dr. MacKinnon was a retired member of the Los Angeles County Medical Association.

Mapes, William D., Roseville. Died July 20, 1978 in Davis, aged 70. Graduate of the University of California Medical School, Berkeley-San Francisco, 1933. Licensed in California in 1946. Dr. Mapes was a member of the Placer-Nevada County Medical Society.

Middleton, Joseph, San Luis Obispo. Died July 25, 1978 in San Luis Obispo, aged 75. Graduate of the University of Southern California School of Medicine, Los Angeles, 1939. Licensed in California in 1939. Dr. Middleton was a retired member of the San Luis Obispo County Medical Society.

Milchen, Carl, West Covina. Died July 8, 1978 in West Covina of metastatic carcinoma, aged 66. Graduate of Marquette University School of Medicine, Milwaukee, 1937. Licensed in California in 1946. Dr. Milchen was a member of the Los Angeles County Medical Association.

Miles, Harold B., Santa Barbara. Died January 9, 1978 of pneumonia, aged 63. Graduate of the University of Cincinnati College of Medicine, 1940. Licensed in California in 1946. Dr. Miles was a member of the Medical Society of Santa Barbara.

Mitchell, Thomas T., San Diego. Died August 2, 1978 in San Diego, aged 70. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1933. Licensed in California in 1933. Dr. Mitchell was a retired member of the San Diego County Medical Society.

Mourer, Harold, Bellflower. Died July 27, 1978 in Tustin, aged 78. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1929. Licensed in California in 1929. Dr. Mourer was a member of the Los Angeles County Medical Association.

Odegard, John K., Walnut Creek. Died August 3, 1978, aged 66. Graduate of Western Reserve University School of Medicine, Cleveland, 1937. Licensed in California in 1938. Dr. Odegard was a member of the Alameda-Contra Costa Medical Association.

Solomon, Seymour J., San Francisco. Died July 1, 1978, aged 61. Graduate of Tufts College Medical School, Boston, 1936. Licensed in California in 1945. Dr. Solomon was a member of the San Francisco Medical Society.

True, William R., Monterey. Died August 2, 1978 in Carmel, aged 62. Graduate of Temple University School of Medicine, Philadelphia, 1947. Licensed in California in 1953. Dr. True was a member of the Monterey County Medical Society.

West, Ernest J., San Jose. Died July 29, 1978, aged 59. Graduate of the Creighton University School of Medicine, Omaha, 1944. Licensed in California in 1945. Dr. West was a member of the Santa Clara County Medical Society.

Westover, Joseph L., Santa Monica. Died May 27, 1978 in Santa Monica of heart disease, aged 63. Graduate of the University of Southern California School of Medicine, Los Angeles, 1943. Licensed in California in 1943. Dr. Westover was a member of the Los Angeles County Medical Association.

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2. Data on file, Hoffmann-La Roche Inc., Nutley, New Jersey 07110.

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Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy, bronchial asthma; in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

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—Other effective compliance enhancers

*By repeated determinations of the basal blood pressure,** and once the medical history, physical examination, including funduscopic and routine laboratory tests,† have been completed, one is usually able to exclude secondary causes and to be reasonably comfortable with a diagnosis of primary or essential hypertension.

**The National Hypertension Program Study Committee, in September, 1972, recommended blood pressures exceeding 140/90 mm Hg be regarded as excessive for adult Americans under age 50. The World Health Committee ceiling has been 160/95 mm Hg.

†Hematocrit, urinalysis, creatinine (or urea nitrogen), triglycerides, cholesterol, uric acid, plasma glucose, serum potassium, electrocardiogram, and chest x-ray.

Please see brief summary of prescribing information on last page of advertisement for warnings, precautions, and adverse reactions.

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References:
1. Wilber JA, Barrow JS: Am J Med, *52*:653-663, 1972.
2. Data on file at Boehringer Ingelheim Ltd.

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Ridgefield, CT 06877

Catapres® brand of clonidine hydrochloride
Tablets of 0.1 mg and 0.2 mg

Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potency. It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established.) These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres (clonidine hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all effects of Catapres (clonidine hydrochloride) overdosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100 and 1000.

For complete details, please see full prescribing information.

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PERCOCET®-5 Tablets (II)

Brief Summary of Prescribing Information

DESCRIPTION Each tablet of PERCOCET®-5 contains 5 mg oxycodone hydrochloride (WARNING: May be habit forming), 325 mg acetaminophen (APAP).

INDICATIONS For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS Hypersensitivity to oxycodone or acetaminophen.

WARNINGS Drug Dependence Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCOCET®-5, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, PERCOCET®-5 is subject to the Federal Controlled Substances Act.

Usage in ambulatory patients Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCOCET®-5 should be cautioned accordingly.

Interaction with other central nervous system depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCOCET®-5 may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in pregnancy Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, PERCOCET®-5 should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children PERCOCET®-5 should not be administered to children.

PRECAUTIONS Head injury and increased intracranial pressure The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions The administration of PERCOCET®-5 or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients PERCOCET®-5 should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

ADVERSE REACTIONS The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation, skin rash and pruritus.

DOSAGE AND ADMINISTRATION Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. PERCOCET®-5 is given orally. The usual adult dose is one tablet every 6 hours as needed for pain.

DRUG INTERACTIONS The CNS depressant effects of PERCOCET®-5 may be additive with that of other CNS depressants. See WARNINGS. 6085 BS

DEA Order Form Required.

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Tablets

PERCOCET®-5

Each tablet contains 5 mg oxycodone HCl (WARNING: May be habit forming) and 325 mg acetaminophen (APAP) (C II)

..FOR THOSE WHO CAN'T TOLERATE ASPIRIN

- □ indicated for moderate to moderately severe pain
- □ contains well-tolerated acetaminophen
- □ provides the effective analgesia of oxycodone
- □ scored tablet permits finer titration
- □ convenient, economical q6h dosage

Please see opposite page for brief summary of prescribing information.

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While therapeutic response remains highly effective, tremor and the modest cardiovascular effects associated with Brethine tend to diminish with continued use. To minimize tremor when initiating therapy, a starting dose of 2.5 mg is recommended. For details, please consult the prescribing information, a summary of which appears on the next page.

Brethine. In the long run, breathing is believing.

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terbutaline sulfate

Now the most widely prescribed bronchodilator tablet in the U.S.

In the long run, breathing is believing.

1. Formgren H: The therapeutic value of oral long-term treatment with terbutaline in asthma. Scand J Respir Dis *56*(6):321-328, 1975.
2. Larsson S et al: Lack of bronchial beta adrenoceptor resistance in asthmatics during long-term treatment with terbutaline. J Allergy Clin Immunol *59*(2):93-100, 1977.
3. Wilson AF et al: Cardiopulmonary effects of long-term bronchodilator administration. J Allergy Clin Immunol *58*(1):204-212, 1976.

Geigy

Brethine®, brand of terbutaline sulfate, Tablets 5 mg., Tablets 2.5 mg. *Before prescribing or administering, please consult complete product information, a summary of which follows:*

Tablets contain 5 mg. (equivalent to 4.1 mg. of free base) or 2.5 mg. (equivalent to 2.05 mg. of free base) of Brethine, brand of terbutaline sulfate.

Indications: As a bronchodilator for bronchial asthma and for reversible bronchospasm which may occur in association with bronchitis and emphysema.

Contraindications: Known hypersensitivity to sympathomimetic amines.

Warnings: *Usage in Pregnancy:* The safety of the use of Brethine, brand of terbutaline sulfate, in human pregnancy has not been established. The use of the drug in pregnancy, lactation, or women of childbearing potential requires that the expected therapeutic benefit of the drug be weighed against its possible hazards to the mother or child.

Usage in Pediatrics: Brethine, brand of terbutaline sulfate, tablets are not presently recommended for children below the age of twelve years due to insufficient clinical data in this pediatric group.

Precautions: Brethine, brand of terbutaline sulfate, should be used with caution in patients with diabetes, hypertension, hyperthyroidism, and a history of seizures. As with other sympathomimetic bronchodilator agents, Brethine, brand of terbutaline sulfate, should be administered cautiously to cardiac patients, especially those with associated arrhythmias. Although the concomitant use of Brethine, brand of terbutaline sulfate, with other sympathomimetic agents is not recommended, the use of an aerosol bronchodilator of the adrenergic stimulant type for the relief of an acute bronchospasm is not precluded in patients receiving chronic oral Brethine, brand of terbutaline sulfate, therapy.

Adverse Reactions: Commonly observed side effects include nervousness and tremor. Other reported reactions include headache, increased heart rate, palpitations, drowsiness, nausea, vomiting, sweating, and muscle cramps. These reactions are generally transient in nature, usually do not require treatment, and appear to diminish in frequency with continued therapy. In general, all the side effects observed are characteristic of those commonly seen with sympathomimetic amines.

How Supplied: Round, scored, white tablets of 5 mg. in bottles of 100 and 1,000 and Unit Dose Packages of 100; oval, scored, white tablets of 2.5 mg in bottles of 100 and 1,000 and Unit Dose Packages of 100.

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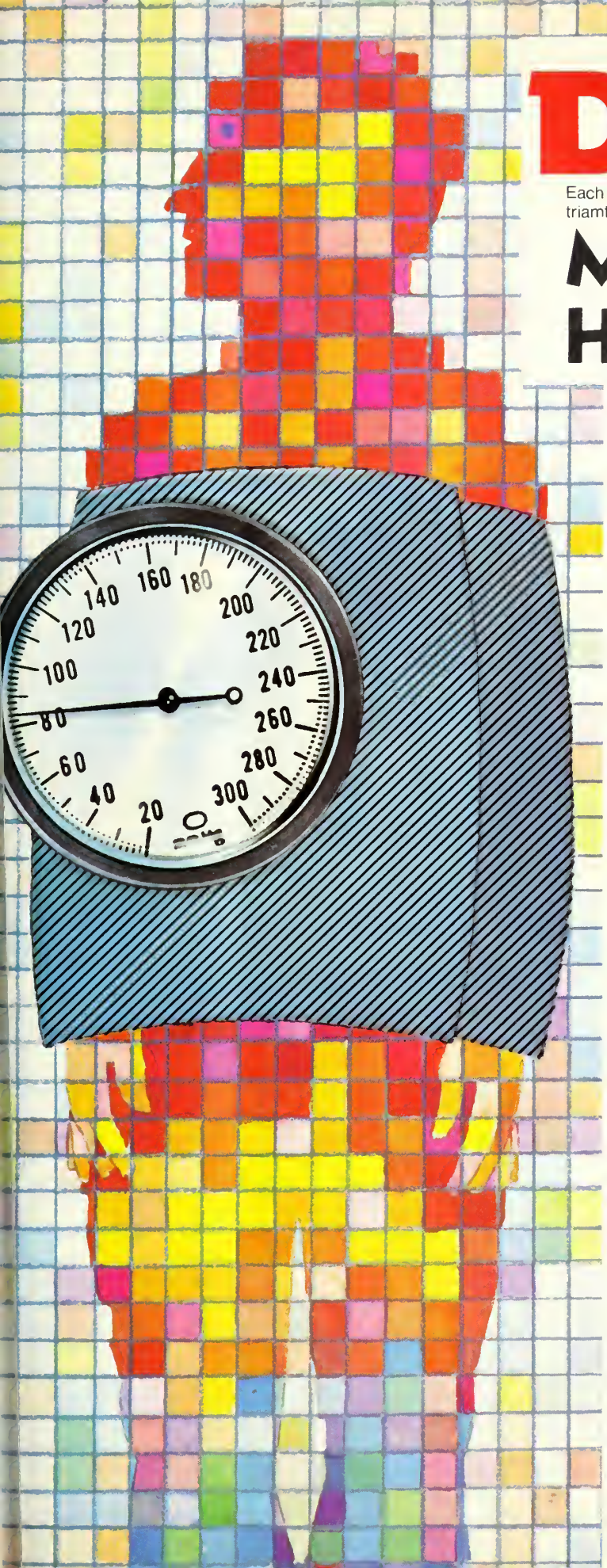

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* **Warning**
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K+ frequently, both can cause K+ retention and elevated serum K+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth, anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

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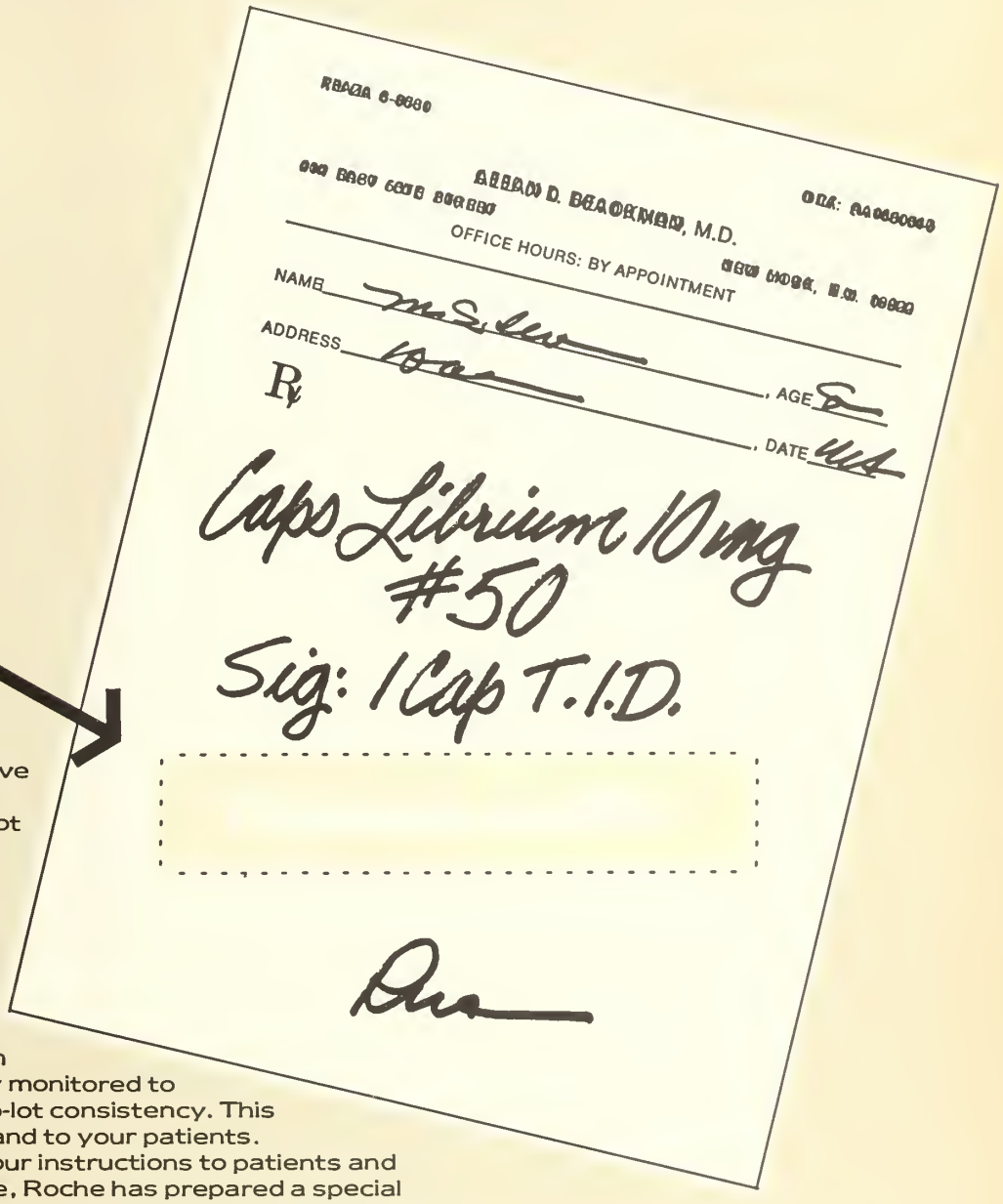

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Please see summary of product information on next page.

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Indications: Relief of anxiety and tension occurring alone or accompanying various disease states. Efficacy beyond four months not established by systematic clinical studies. Periodic reassessment of therapy recommended.

Contraindications: Patients with known hypersensitivity to the drug.

Warnings: Warn patients that mental and/or physical abilities required for tasks such as driving or operating machinery may be impaired, as may be mental alertness in children, and that concomitant use with alcohol or CNS depressants may have an additive effect. Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported.

Usage in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (e.g., excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.

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THE WESTERN
Journal of Medicine

Refer to: Gelpi AP: Inflammatory bowel disease among college students. West J Med 129:369-373, Nov 1978

Inflammatory Bowel Disease Among College Students

ARMAND P. GELPI, MD, *Stanford, California*

Of 52 student patients with chronic inflammatory bowel disease who were observed at Stanford University over a three-year period, 16 had Crohn disease, 17 had ulcerative colitis and 19 had ulcerative proctitis. Patients with ulcerative colitis had relatively few complications. During the study period, only two students from the entire group of 52 were obliged to interrupt college attendance because of bowel disease or complications. Of the patients, 33 were first observed on remission or attained remission during the three-year observation period. Incidence and prevalence rates for Crohn disease and ulcerative colitis were comparable with age-specific rates from other published studies. At Stanford, the high reported frequency of proctitis, which exceeded that of proximal ulcerative colitis, was possibly a reflection of the diagnostic zeal with which patients with rectal bleeding were evaluated at the student health service.

At Stanford University, chronic inflammatory bowel disease (IBD) ranks with hypertension, peptic ulcer and juvenile onset diabetes mellitus as one of the disorders with the potential for significant disability and serious complications that are most frequently encountered among college students. This report summarizes recent experience with Crohn* disease (CD), ulcerative colitis (UC) and nonspecific ulcerative proctitis (UP) in a college population and identifies clinical and epidemiological trends for comparison with similar material from selected recent publications.

Data from numerous sources indicate that adolescents and young adults are at greatest risk for the development of IBD, and recent encounters with IBD among students at Stanford student health service reinforce this view. However, most published studies have focused on patient data derived from large clinics and hospitals, with the unavoidable tendency to record instances only of more severe or more complicated disease. For this reason alone, it appeared useful to look at the problem of IBD in a primarily outpatient setting, which is characteristic for most patient encounters in busy health services at major universities.

Subjects and Methods

From January 1, 1975, through December 31, 1977, 52 Stanford students were identified with

*The Western Journal's style regarding eponyms is that they are not written in the possesive form; therefore, Graves disease, Ewing sarcoma and Paget disease. An explanation may be found on page 78 of the July 1978 issue.

From the Cowell Student Health Center, Stanford University, and the Palo Alto Medical Clinic, Palo Alto, California.

Submitted, revised, May 8, 1978.

Reprint requests to: Armand P. Gelpi, MD, Cowell Student Health Center, Stanford University, 606 Campus Drive, Stanford, CA 94305.

ABBREVIATIONS USED IN TEXT
CD = Crohn disease
IBD = inflammatory bowel disease
UC = ulcerative colitis
UP = ulcerative proctitis

the diagnosis of IBD. During this period, the student body approximated 12,500, including graduate students. Conventional diagnostic criteria[1] included characteristic sigmoidoscopic and radiologic features and, in certain instances, supportive histologic findings from biopsy material obtained at laparotomy or from rectal mucosal biopsy. In the case of UP, appropriate histories were taken to exclude the possibility of rectal trauma, and rectal cultures were ordered to exclude enteropathic infection, primarily gonococcal proctitis.

Criteria for remission among those patients with CD and UC included normal bowel habits, freedom from tenesmus and abdominal pain, absence of hematochezia, the absence of fever and other systemic complaints and, finally (when applicable), a sigmoidoscopic examination showing the absence of bleeding, exudate, friability and ulceration. The presence of mucosal thickening or granularity was not necessarily regarded as an indication of disease activity. The criteria for remission among patients with UP were absence of hematochezia and proctoscopic evidence of a normal rectal mucosa, except for thickening or granularity.

Point prevalence data were based on documentation of those students with IBD who were registered at Stanford at the conclusion of the first academic quarter (October through December) of 1975, 1976 and 1977. Incidence was obtained from tabulation of all newly diagnosed cases of IBD seen during the study period. Unless otherwise specified, both prevalence and incidence are expressed here as the number of cases per 100,000 population for comparison with data in certain publications dealing with the epidemiology of IBD.

Clinical Profile

There were 17 patients with CD, 16 with UC and 19 with UP. Clinical features of 21 of the total group have been reported in a preliminary publication.[2] Ten patients with CD were in remission at the time they were entered into the study or attained remission in the interval from 1975 to 1977. In four patients, CD was active upon entry into the study or was reactivated during the study period. The status of three patients in this group is uncertain because of inadequate follow-up. Surgical procedures (all small-bowel resection) were required for four patients with CD, with additional partial colectomy necessary for two of them. Most patients in this group have been treated with salicylazosulfapyridine (Azulfidine®) or corticosteroids (or both); only one was obliged to interrupt college attendance because of CD or its complications during the observation period. Complications occurred more often with CD than with UC, but this difference was not significant, $X^2 = 2.12$, $P > 0.10$ (Yates' correction). With one exception, all complications occurred in patients with colonic disease, with or

TABLE 1.—*Clinical Observations: Inflammatory Bowel Disease in Stanford Students*

	Crohn Disease	*Ulcerative Colitis*	*Ulcerative Proctitis*	*Total*
Sex				
Male	11	10	14	35
Female	6	6	5	17
*Age**				
Mean (years)	23.0	22.0	24.0	24.0
Range (years)	18-35	17-30	19-36	17-36
Site				
Ileum alone	4	..	..	4
Ileum, jejunum	1	..	..	1
Ileum, jejunum, colon	1	..	..	1
Colon alone	4	16	..	20
Ileum, colon	7	..	..	7
Rectum alone	..	..	19	19
Complications				
Spondylitis	2	1	..	3
Perianal disease	1	..	..	1
Hemolytic anemia	..	1	..	1
Pancreatitis	1	..	..	1
Bowel perforation	1	..	..	1
Enterovesical fistula	1	..	..	1
Lactose intolerance	1	..	..	1
Medication				
Corticosteroids (systemic)	13	7	..	20
Corticosteroids (topical)	1	1	9	11
Azulfidine®	9	10	8	27
Imuran®	..	1	..	1
Surgical Procedure				
Small-bowel resection	4	..	..	4
Colectomy	2	2	..	4
Status				
Remission	10	13	10	33
Active	4	3	8	15
Unknown	3	..	1	4

*Age at time of inclusion in study.

without small-bowel involvement. Recurrent pancreatitis in one patient was believed to be not necessarily related to the bowel disorder. The clinical features of IBD in Stanford students are summarized in Table 1.

The 16 patients with UC had fewer complications than did those who had CD, but otherwise the course of disease was similar. During the study period, 13 achieved or maintained remission; only one of this group was obliged to interrupt college attendance. One patient had undergone colectomy before inclusion in the study, and during the summer of 1976 another student underwent colectomy because of smoldering disease and extensive pseudopolyposis.

As a group, perhaps the most interesting were the 19 patients with UP. All these patients had the symptom of intermittent or sustained rectal bleeding without a change in bowel habits; they had no systemic manifestations, and only occasionally had they experienced abdominal discomfort or tenesmus. Proctoscopic examination showed one or more areas of mucosal abnormality, but these were sharply confined to the rectum. Frank ulceration was unusual: in most patients there was evidence only of granularity, friability, adherent mucopus and contact bleeding. In each of these patients, a length of normal proximal bowel could be seen, and x-ray examination of the colon showed a normal proximal mucosal pattern. None of these patients showed evidence of proximal extension during the limited period of observation, and ten attained or sustained remission during the study period; one had several relapses.

Age at onset was available for 11 patients with CD, 14 patients with UC and 17 patients with UP. The mean age at onset was 21 years (CD group), 19 years (UC group) and 23 years (UP group). Mean age at the time of inclusion in the study was 23 years (CD group), 22 years (UC group) and 24 years (UP group).

Epidemiology

In the group of patients with IBD, the ratio of men to women was 2.05. The ratio of men to women for the Stanford study body was 2.04, so that the adjusted sex ratio for incidence of IBD is 1.00. There is considerable spread in the incidence/prevalence ratios for IBD: 1/11 for CD, 1/4.2 for UC and 1/2 for UP (Table 2). These ratios primarily reflect comparable prevalence but pronounced differences in incidence among the three groups. Although CD was the most prevalent type of IBD seen over the three-year period, there was an unexpectedly high incidence of ulcerative proctitis.

There were two black patients with IBD: one with CD and one with UC. There was one second-generation Japanese patient with UP, one Iranian with UC, and a Saudi Arabian with UP. There were 11 Ashkenazi Jewish patients in this series at a time when Jewish representation in the student body was approximately 1,100. The comparative prevalence of IBD between Jews and non-Jewish students was five and two, respectively, per 1,000. This difference is not significant ($X^2 = 2.45$, $P > 0.10$), but the trend is consistent, with a number of independent observations on the rather high prevalence of IBD among Ashkenazi Jews.

Comment

In 1963, Ray[3] and Larsh[4] noted increasing prevalence of ulcerative colitis among students at Northwestern University and at the University of Chicago, and subsequently Ray summarized experience with UC affecting students at Northwestern University over a 20-year period.[5] She observed a prevalence ranging between 12 and 15 on a year-to-year basis. These are the only previously published studies of IBD confined to the college setting, and they do not consider the problems of CD and UP.

Of particular relevance to the study of inflam-

TABLE 2.—*Cases of Inflammatory Bowel Disease at Stanford, 1975-1977*

	Incidence				*Prevalence*			
	Crohn Disease	*Ulcerative Colitis*	*Ulcerative Proctitis*	*Total*	*Crohn Disease*	*Ulcerative Colitis*	*Ulcerative Proctitis*	*Total*
1975	2	2	1	5	12	9	4	25
1976	1	5	11	17	13	13	11	37
1977	.	.	2	2	8	8	14	30
Rate*	8	19	37	64	88	80	77	245

*Rate is the mean number of cases per year $\times \frac{100,000}{12,500}$ expressed as the nearest whole number.

matory bowel disease among young adults seen in college health services are the recent epidemiologic data from a series of 1,400 patients observed at the University of Chicago School of Medicine: The authors of the report on these data were able to show a striking correlation between the prevalence of IBD and the attainment of higher education.[6] Of those patients with IBD who were more than 25 years old, 59.1 percent had completed four or more years of college as compared with a national average of 7.7 percent for the same age group in the general population.

Experience with IBD at Stanford has shown a pattern of disease with relatively few complications, minimal short-term disability and a high frequency of remission. For comparison, the study of Patterson and co-workers[7] of a group of patients with ulcerative colitis that began in childhood or adolescence emphasized the severity of the disease, a formidable array of complications, and a mortality of 14 percent in a series of 43 patients.

Despite the limitations of certain epidemiologic surveys of IBD, primarily the problem of selection of patients with more severe disease, data of several recent publications are useful for comparison with those of the small Stanford series. Age-specific prevalence and incidence rates are available from a few European and American sources. A study in Oxford, England,[8] showed cumulative prevalence rates for ulcerative colitis in the age groups 14 to 24 years and 25 to 34 years of 18.2 and 65.9, respectively; the corresponding incidence rates were 4.0 and 10.9. A survey in Copenhagen, Denmark,[9] showed the prevalence of ulcerative colitis as 34 in the second and third decades, with an incidence of 8.6. A study of Crohn disease in Malmo, Sweden, showed an incidence of 18 in the second and third decades.[10] In Rochester, Minnesota, the incidence of inflammatory colon disease (UC and CD) was found to be 21 in the third decade.[11] For obvious reasons, comparisons between disease rates at Stanford and the IBD rates from the studies cited above can be only rough approximations. However, it appears that the prevalence and incidence rates for Crohn disease and ulcerative colitis in a small, well-defined college population are comparable with and possibly exceed rates that are adjusted for age from several more heterogeneous populations of northern Europe and the United States. Extrapolating from the data of Rogers and associates[6] on the association of IBD with the degree of educational achievement, it appears that the population is stratified with respect to IBD: 73.1 percent of persons with IBD have attained some college education but represent only 16.5 percent of the total population in regard to educational status. The implication is that there is a dispersed population of patients with disabling IBD who have been unable to attend college and a small proportion who would not attend college for reasons not related to health status, and, further, that true prevalence and incidence rates may be lower for young adults than has been suggested by either the Stanford study or other recent epidemiologic surveys.

The unusually high frequency of proctitis at Stanford is matched by the proportion of patients with proctitis in a series of 108 patients with inflammatory colon disease who were diagnosed in Rochester, Minnesota, from 1935 through 1964.[11] Fifty-eight of these patients had either transient or chronic proctitis. In contrast, Farmer and Brown,[12] in a study of 1,258 patients with ulcerative colitis, found only 52 (4 percent) with disease limited to the rectum. Sparberg and co-workers[13] culled 45 patients with rectal disease only, from a group of 1,181 persons with ulcerative colitis; this again represented 4 percent of the total. In the Stanford study, proctitis constitutes more than 50 percent of the group with ulcerative colitis. There is doubtless some selective bias in the diagnosis of proctitis at this university, where virtually every patient with minor rectal bleeding is examined by proctoscope. Also, there is some question whether nonspecific proctitis represents a mild form of ulcerative colitis. Therefore, the experience at Stanford could reflect the timely diagnosis of a form of IBD that is genuinely on the increase, as the high incidence/prevalence ratio would suggest. On the other hand, Lennard-Jones and co-workers[14] found that eight of 69 patients with proctitis went on to develop proximal disease, and Sparberg and associates[13] found that ten of 29 patients with proctitis who were followed for five or more years had proctoscopic evidence of proximal extension. Nine of 21 in this group showed extension into the sigmoid in follow-up x-ray studies; only three showed progression above the sigmoid. These published reports certainly suggest that ulcerative proctitis is a mild expression

of a potentially serious and more extensive colonic disease.

Experience with inflammatory bowel disease at Stanford warrants the conclusions that ulcerative proctitis may be more frequent in young adults than has been previously appreciated and that extended studies of inflammatory bowel disease in college populations may afford a more balanced view of the natural history of both Crohn disease and ulcerative colitis together with useful information on the effects of socioeconomic, cultural and ethnic stratification on the expression of IBD.

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Techniques of Needle Spinal Insertion

ONE OF THE TRICKS that I try to teach is the slow insertion of a subarachnoid needle, identifying every structure as it is perforated with the needle. This gives one a very clear idea of where the needle is before perforating the dura. Most people tend to jab with the needle which deprives you of the feel of the needle. Another trick is to control the direction of the needle. For example, the puncture should be made close to the caudal end of the interspace and the needle should be inserted at a 90-degree angle to the skin, which we all know is too wide an angle, but in having hit the lamina, which is your next stop on your way to the subarachnoid space, the needle is pulled back a little and reinserted in a more caudal fashion until one gets back by the lamina and falls into the epidural space and into the subarachnoid space. In other words, not only should the insertion be controlled, but the direction of the needle should be controlled too, and every attempt must be made to identify every structure.

—WILLIAM GOTTSCHALK, MD, *Chicago*

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Carcinoembryonic Antigen in Patients With Breast or Colon Cancer

YEU-TSU N. LEE, MD, *Los Angeles*

The rationale and results of clinical use of carcinoembryonic antigen (CEA) tests in patients with carcinoma of the breast and colon deserve review. Plasma CEA levels have been found to correlate with the extent of tumor invasion and site of metastatic spread, and CEA titers have diagnostic and prognostic value. Although postresectional serial CEA testing is not as useful in cases of breast carcinoma, in cases of carcinoma of the colon it may indicate recurrence or progression of the lesion. However, there are limitations and CEA results should be interpreted in conjunction with other clinical information.

THE TERM carcinoembryonic antigen (CEA) was first used in 1965 by Gold and Freedman[1] to describe an antigen present in extracts of colonic adenocarcinoma and digestive organs of human embryos. When they noted elevated levels of CEA in plasma in 36 of 37 advanced colon carcinoma cases, it was hoped that a specific test for cancer of the colon had been discovered. This proved not to be the case, as subsequent investigation indicated the presence of CEA in nonentodermal tumors as well as in various nonneoplastic diseases.

CEA is a glycoprotein and consists of 45 percent protein and 55 percent carbohydrate. It has a molecular weight of about 200,000 with beta-electrophoretic mobility in immunoelectrophoresis. CEA is a constituent of the mucus which is normally secreted into the lumen by epithelial cells of the gastrointestinal tract. As the normal tissue architecture is disrupted, the CEA is released into underlying tissue and diffuses into the vascular or lymphatic channels. Rapid cellular proliferation and disruption of basement membranes explains the presence of elevated circulating CEA levels in patients with entodermal and nonentodermal malignancies, with various nonmalignant metabolic or inflammatory diseases,[2] in surgical trauma and in cases of heavy smoking.[3]

From 1971 to 1974, the CEA test was evaluated extensively in a collaborative study of 35,000 assays in more than 11,000 patients from over 100 medical institutions. The result showed that 97 percent of healthy nonsmoking subjects had titers of 2.5 ng per ml or below, none above 5 ng per ml (Table 1). Even among chronic smokers (more than one pack a day for at least ten years), 4 percent had CEA titers above 5 ng per ml and only 1 percent over 10 ng per ml. After cessation of smoking, elevated CEA levels declined to nonsmoker range within three months.[3]

In the absence of malignant disease, CEA titers greater than 5 ng per ml were associated with such conditions as pulmonary emphysema, alcoholic cirrhosis, ulcerative colitis, regional ileitis, granulomatous colitis, gastric and duodenal ulcers,

From the Department of Surgery, University of Southern California Medical School and the Tumor Surgery Service, LAC-USC Medical Center, Los Angeles.

Submitted, revised, May 1, 1978.

Reprint requests to: Yeu-Tsu N. Lee, MD, Dept. of Surgery, USC School of Medicine, 1200 North State Street, Los Angeles, CA 90033.

TABLE 1.—*Distribution of CEA Levels Among 2,107 Healthy Volunteers**

Condition	Number of Patients	CEA Levels <2.5 ng per ml (Percent)	>2.5 ng per ml (Percent)	>5 ng per ml (Percent)	>10 ng per ml (Percent)
Pregnancy	360	96	4	1	0
Nonsmokers	892	97	3	0	0
Former smokers .	235	93	6	2	1
Presently smoking	620	81	18	4	1
	2,107	92	8	2	0.5

CEA = Carcinoembryonic antigen

*Adapted from CEA-Roche Assay, Hoffman-La Roche, Inc. 1974[8]

TABLE 2.—*Distribution of CEA Levels Among 3,340 Patients With Nonmalignant Disease**

Diagnosis	Number of Patients	CEA Levels <2.5 ng per ml (Percent)	>2.5 ng per ml (Percent)	>5 ng per ml (Percent)	>10 ng per ml (Percent)
Breast lesions ...	115	85	15	4	0
Duodenal ulcer .	166	70	30	8	2
Gastric ulcer ...	94	55	45	16	1
Cholecystitis	39	77	23	6	1
Colorectal polyps	90	81	19	4	1
Diverticulitis	84	73	27	7	2
Ulcerative colitis .	146	69	31	13	5
Regional ileitis ..	126	60	40	13	2
Granulomatous colitis	59	53	47	20	5
Alcoholic cirrhosis	120	29	71	26	2
Pulmonary emphysema ...	49	43	57	20	4
Others†	2,281	69	31	8	1
	3,340	67	33	9	1

CEA = Carcinoembryonic antigen

*Adapted from CEA-Roche Assay, Hoffman-La Roche, Inc. 1974[8]

†Major categories include heart disease (289), diabetes (230), myasthenia gravis (183), hypertension (156), osteoarthritis (112), pancreatitis (95), and bronchitis (61).

colorectal polyps and diverticulitis (Table 2). It is important to note that most of the "false-positive" elevations of circulating CEA levels tend to be lower than those found in cancerous conditions (Table 3). And many of the nonmalignant conditions associated with positive assays show transient rather than persistent elevations of CEA levels. For instance, CEA titers in patients with nonmalignant colonic polyps or inflammatory disease usually drop to below 2.5 ng per ml when the polyps are resected or diseases are in remission.[4,5]

More than any other common benign disease, liver disease (especially severe alcoholic cirrhosis) may cause mildly elevated CEA levels. Perhaps half the patients with benign obstructive jaundice have elevated CEA titers which fall after surgical

TABLE 3.—*Distribution of CEA Levels Among 1,343 Patients With Carcinoma (All Stages)**

	Number of Patients	<2.5 ng per ml (Percent)	>2.5 ng per ml (Percent)	>5 ng per ml (Percent)	>10 ng per ml (Percent)
Entodermal carcinoma	**859**	**27**	**72**	**48**	**31**
Gastric carcinoma	79	39	61	29	19
Colorectal carcinoma	544	28	72	49	35
Pulmonary carcinoma	181	24	76	50	25
Pancreatic carcinoma	55	9	91	61	35
Nonentodermal carcinoma	**468**	**52**	**48**	**22**	**9**
Breast carcinoma .	125	53	47	27	14
Head and neck carcinoma	128	48	52	19	5
Other carcinoma .	215	53	47	21	9
Overall	1,343	35	65	38	23

CEA = Carcinoembryomic antigen

*Adapted from CEA-Roche Assay, Hoffman-La Roche, Inc. 1974[8]

release of the obstruction, provided persistent biliary inflammation or liver abscess does not supervene. Some of the elevated CEA levels in patients with inflammatory bowel disease may be due in part to coexisting liver disease. Elevated levels commonly accompany alcoholic pancreatitis. Therefore, correct clinical interpretation requires concomitant assessment of liver status.[6,7]

In January 1974 reagents for the CEA assay (patented by Hoffman-La Roche) became the first biological substances to be approved by the Food and Drug Administration as products for *in vitro* cancer diagnosis. In the CEA-Roche radioimmunoassay procedure the assay is capable of measuring plasma levels as low as 0.5 ng per ml. The reproducibility of the test is as follows: A standard deviation of approximately 0.5 ng per ml in the 0 to 5 ng per ml range, approximately 1.0 ng per ml in the 5 to 10 ng per ml range and approximately 2.0 ng per ml in the 10 to 20 ng per ml range.[8]

In patients with elevated CEA levels, the distribution of blood groups and secretor status showed no correlation with the frequency distribution of abnormal results.[9,10] Go[11] found that other factors—sex, age, time of day when the blood sample was drawn, and the presence or absence of family history of cancer—do not influence the CEA level. Among 17 patients with colorectal carcinoma, there was no correlation between tumor CEA and serum CEA levels.[12]

It is emphasized that the CEA test should not be used for screening purposes to detect cancer in the general population. CEA titers are not an absolute test for malignancy, nor for a specific type of malignancy. And CEA levels less than 2.5 ng per ml do not preclude the presence of primary, recurrent or metastatic cancers (Table 3). However, very high CEA levels (above 20 ng per ml) usually indicated metastatic disease.

In patients with documented cancer, it is reported that monitoring the level of CEA in the circulation before and after therapy may be useful. In general, decreases in CEA titers were associated with effective therapy. A persistent increase in titers was associated with a lack of response to therapy or a recurrence of disease; in some cases, the titer rise preceded clinical signs for several months. Since CEA tests have been used widely for purposes of follow-up studies in patients with malignant lesions of the breast and colorectum, their rationale, results and limitations are reviewed here in detail.

CEA in Patients With Breast Cancer

In the Roche collaborative study, among 115 patients with benign breast diseases, 15 percent had titers of CEA above 2.5 ng per ml, none above 10 ng per ml (Table 2). Among 125 patients with various stages of carcinoma of the breast, 47 percent had CEA levels above 2.5 ng per ml, 27 percent above 5 ng per ml, and 14 percent above 10 ng per ml (Table 3). In general, CEA levels in patients with breast cancer were lower than those seen in patients with gastrointestinal cancer. Plasma CEA levels did not correlate with the menstrual status of the patient, nor with the size of the primary lesions,[13] nor the presence of estrogen receptor in the tumors.[14]

Subsequently, it was found that the proportion of elevated CEA levels increased with increased tumor spread.[15] More patients with lymph node involvement had abnormal levels of CEA than those with lesions limited to the breast; and in over 70 percent of the patients with distant metastasis the concentrations were increased. The incidence of elevated CEA values varied according to the site of metastasis. It ranged from 41 percent in patients with soft-tissue metastasis, 64 percent for osseous, 83 percent for pulmonary, to 93 percent for hepatic metastasis.[16] Pronounced elevation of CEA (greater than 25 ng per ml) was observed most frequently in patients with hepatic and osseous metastasis.[17] In patients with recurrences in the chest wall only there were normal CEA titers, suggesting that the amount of tumor present was usually much less than in patients with visceral involvement.[18] Strangely, when metastatic lesions occur at three or more organ sites, there is a decreased incidence in quantitative CEA levels.[17] This is similar to the situation in patients with carcinomas of colon or lung where the CEA level sometimes decreases with very advanced disease.[19]

The titer of CEA in patients with early or localized breast cancer, before or after mastectomy, was found to be similar to that in healthy women.[9,20] There was no correlation between the actual levels of CEA before mastectomy and recurrence during follow-up. However, CEA determinations ten days after mastectomy had prognostic importance: 20 percent of patients who had CEA values below 2.5 ng per ml had recurrence of the disease in two years as compared with a 65 percent recurrence rate in women with higher CEA levels.[20] The timing of postoperative CEA test may be critical, because Tormey and co-workers[17] found no direct correlation between postoperative CEA changes and the presence or absence of relapse. They obtained postoperative CEA values at one or more months and found that 23 percent had elevated levels (more than 2.7 ng per ml in nonsmokers and 5 ng per ml in smokers). Chu and Nemoto[16] obtained blood samples at 4 and 14 days after mastectomy. They found an increase of CEA values in nine of 21 patients immediately following surgical operation. A similar transient rise was also detected in patients with other tumors and with benign diseases. They found that CEA levels in patients who had undergone mastectomy did not reflect the presence or absence of early metastasis.

In patients with advanced mammary carcinoma receiving chemotherapy or hormonal therapy, some investigators reported that a good clinical response to therapy was mirrored by a fall of CEA values to normal levels.[17] Others found good correlation only among patients with pronounced regression or progression of the disease, but the overall correlation was not good enough.[14,16] A high initial CEA level at the outset of therapy did not necessarily imply a poor prognosis, and a low initial CEA level did not guarantee a good response to therapy.[21] Tormey and co-workers[17] found that pretherapy CEA levels of over 5 ng per ml were

associated with low response rates and early failure of chemotherapy. The prognostic value of the initial CEA level appeared to be independent of other clinical features such as menopausal status and sites of involvement.

CEA in Patients With Cancer of the Colon

General Remarks

In initial studies, CEA values in patients with cancer of the colon were reported as being 97 percent positive.[22] Such findings were confirmed in patients with "overt" cancer of the colon, many of whom had metastases. In later expanded studies, however, patients with earlier stages of the disease were included, resulting in a fall of positive assays to 72 percent.[6] The number of positive assays fell even further to 59 percent in patients seen preoperatively,[23] but rose to almost 100 percent among patients with liver metastasis.[7] Therefore, CEA levels vary with the extent of disease.

In two series, CEA values were greater than 2.5 ng per ml in 14 to 18 percent of patients with Duke A lesions, in 53 to 62 percent with B, in 60 to 65 percent with C, and in 79 percent of patients with D lesions.[24,25] Therefore, a preoperatively negative assay (less than 2.5 ng per ml) does not exclude the diagnosis of cancer, but it does make the diagnosis of metastasis less likely. The titers of CEA did not correlate directly with the size of the tumor.[4] And it was suggested that the neoplastic cells differed morphologically and could be divided into two types: (1) tissues in which malignant cells secreted CEA in greater or lesser quantity and (2) tissues in which CEA was localized in the cells.[29]

Within every particular Duke stage, there was a tendency for the higher plasma value to be associated with a worse prognosis.[26,27] With a preresectional CEA value of less than 2.5 ng per ml, recurrence has been rare (5 percent). But, when the pretreatment CEA value was greater than 7 ng per ml, in most patients (seven of nine) the disease recurred within eight months.[28] Lo Gerfo and Herter[26] found that the chance of recurrence or death within three years is 1.8 times greater in patients who had elevated preoperative CEA values. The prognosis for recurrence is greater in patients with elevated preoperative values, regardless of the stage of the disease.

Martin and co-workers[4] noted an excellent correlation between plasma CEA levels and grade of tumor of the colon: Well-differentiated tumors showed higher titers. (Denk and co-workers[30] found well-differentiated tumors of the colon contained more CEA.) However, Go[11] said serum CEA levels were not influenced by the grade of differentiation of the tumor. Bivins and associates[31] noted that plasma CEA correlated better with vessel invasion and necrosis than with other histologic characteristics of cancer of the colon. Zamcheck and co-workers[32] found CEA levels tended to be elevated when blood vessel, lymphatic and perineural invasion was present. An inverse correlation was also noted between the preoperative CEA level and the degree of tumor differentiation, and lymphocyte and plasma cell infiltration in the primary tumor of the colon. They suggested that the combined measures had more prognostic values than any single one alone.

It is interesting to note that a higher percentage of patients who had cancers of the colon on the left side (splenic flexure, descending colon and sigmoid) had detectable levels of CEA than patients who had cancer of the colon on the right side (cecum, ascending colon, and hepatic flexure). For all stages of the disease, overall incidence of increased values was 47 to 59 percent versus 28 to 41 percent.[4,25] However, patients with carcinomas of the rectum had the lowest incidence of elevated values of CEA (24 percent). Sugarbaker[33] showed that pretreatment CEA titers in patients with obstructive colorectal cancer were unusually high. And relief of obstruction alone produced pronounced reduction in circulating CEA levels.

Resectable Lesions

Thomson and co-workers[22] reported five cases in which preoperative elevated CEA determinations fell to normal levels after complete resection of the colonic cancer. Many other investigators have confirmed this finding. Lo Gerfo and associates[34] found two patterns of postoperative fall in CEA levels after curative surgical operation. In one group an immediate fall to a nadir occurred within two to four days. In another group, the postoperative nadir occurred between 10 and 18 days. Others[18] have noted a more variable pattern of decline of CEA values after curative resection, including a rise in CEA values from normal to abnormal levels. During two or three weeks after operation, CEA produced by the resected tumor might still be present in the circu-

lation; therefore, CEA test is of limited usefulness within 30 days after curative surgical operation. By 60 to 90 days there was a definite difference between those patients who remained free of disease and those who relapsed.[28]

In a prospective study of 102 patients after potentially curative resections of colorectal cancer, in 18 patients elevated levels of circulating CEA developed 2 to 42 (mean 16) months later. Six of these 18 patients had progressively rising CEA values, and all six subsequently had recurrences. It is significant that elevations in CEA were noted up to 29 months before clinical evidence of recurrence.[10] In six patients with stable elevations and in six with transiently elevated levels cancer did not develop. None of the 84 patients with CEA levels of less than 2.5 ng per ml had evidence of recurrence during the follow-up period. However, two patients with levels consistently under 2.5 ng per ml were found to have small second primary cancers of the colon at sites distant from the first lesion.

Mach and co-workers[35] and Mackay and associates[27] confirmed that rising CEA levels preceded clinical evidence of recurrence of cancer by two to 18 months. It was noted that an incomplete drop of circulating CEA levels one month after operation had a bad prognostic significance. However, the reverse is not true.

Holyoke and associates[28] emphasized that at least two consecutive elevated CEA values, the second being higher, must be obtained before considering possible progression of disease. They found elevated plasma CEA levels in 90 percent of the patients at time of recurrence; in about a third of the patients, CEA values rose six or more months before the relapse was otherwise detectable. Alkaline phosphatase and transaminase values correlated poorly with the disease state or the CEA results. But even with sequential testing at one to three month intervals and excluding patients with clear-cut associated benign causes, they encountered false positive results in 10 to 16 percent of their patients.[36]

Rieger and Wahren[37] pointed out that in 70 percent of 20 patients with local recurrence without distant metastases, who were potential candidates for a reoperation for cure, plasma CEA values were raised. However, Moertel and associates[38] reported that only nine among 36 patients (25 percent) with proven local recurrent or residual malignant disease in the pelvis after resection of colorectal cancer had abnormal CEA levels greater than 5 ng per ml.

Sugarbaker and associates[39] compared the relative value of monthly CEA tests, three-monthly physical examinations plus stool test for occult blood, and six-monthly tests of hematocrit, alkaline phosphatase, chest and barium enema roentgenograms, liver scan and sigmoidoscopy in detecting recurrent colorectal cancer. In 12 of the 33 patients studied prospectively recurrent disease developed: in 5 the earliest indications were symptoms or physical findings, in 4 progressively rising CEA titers, in 2 both symptoms and the CEA test, in one surgical reexploration. Among the four patients in whom CEA values rose significantly before other evidence of recurrence appeared, two had retroperitoneal masses and one had liver metastasis. Among 16 patients who had persistent elevation of CEA following surgical operation, 11 remained clinically disease-free after 24 to 48 month (mean 31). Therefore, they concluded that CEA, and other laboratory or radiological tests, should not be a substitute for careful clinical follow-up.

Many surgeons have proposed the use of a second-look operation in patients who had a curative resection and in whom elevation of circulating CEA persists without clinical signs of tumor recurrence. Martin and co-workers[40,41] suggested that each laboratory should establish 95 percent confidence limits at various CEA levels, so that any value that was two standard deviations greater than the previous test would mean very significant elevation. In three reports utilizing second-look operations for patients with rising CEA values, in 45 of 51 patients (88 percent) recurrent disease was found.[7,39,42] In six of 22 patients (27 percent), tumors were resectable.[40] Meeker[43] calculated that serial CEA tests, at $30 per single test and with a cost-benefit ratio of about $3,300 per patient benefited, are indicated in follow-up studies of patients after curative resection of cancer of the colon.

Unresectable or Advanced Lesions

In patients who had elevated CEA levels caused by localized disease and who received radiation therapy, a pronounced fall in serial CEA levels was noted if all CEA-producing tumor was localized within the radiation portal.[44] Persistently low serial CEA titers after irradiation therapy correlated with control of the disease. Rising serial

CEA levels in patients with known metastatic gastrointestinal cancer and treated with chemotherapy correlated with progression of the disease.[28] Persistently low, especially undetectable values were a favorable prognostic sign in patients with cancer of the colon. High or rising levels were unfavorable.[45] The limited effectiveness of chemotherapy for gastrointestinal cancer precluded any definitive conclusion regarding the effect of chemotherapeutically induced tumor regression on CEA levels, although there was suggestive evidence that CEA correlated with remission.

Ravry and co-workers[19] confirmed these general observations, but noted day-to-day variation of CEA levels in 35 percent of their patients. It is also well-known that some cancers of the colon do not produce CEA, and such lesions may deteriorate without a concomitant rise in blood CEA levels.[11] About 10 to 33 percent of patients with extensive recurrent disease do not have elevated circulating CEA titers.[27,44] And, in some patients, a preterminal fall rather than a rise in CEA levels may occur. Therefore, it is emphasized that one needs to interpret CEA values cautiously, and only in context with the overall clinical and laboratory findings.

Conclusion

Carcinoembryonic antigen (CEA) is a glycoprotein which is normally secreted into the lumen by epithelial cells of the gastrointestinal tract. Blood (plasma) CEA levels have been found to be elevated in patients with various non-malignant, metabolic, or inflammatory diseases, in surgical trauma, and in cases of heavy smoking. Some malignant tissues do not release CEA. In general, high CEA levels above 20 ng per ml usually indicated metastatic disease. However, a negative test of CEA does not rule out the presence of metastatic disease.[46]

In patients with carcinoma of the breast, the proportion of elevated CEA levels increases with increased tumor spread, and varies among different sites of metastasis. Among patients with operable breast carcinomas, the actual levels of CEA before mastectomy do not correlate with the incidence of recurrence during follow-up. Some authors reported that patients with an elevated CEA test ten days after mastectomy had a higher chance of recurrence, while others noted no direct correlation between postoperative CEA changes and the presence or absence of relapse. In patients with advanced lesions who received chemotherapy or hormonal therapy, some investigators reported a good correlation between response to therapy and decreased CEA levels, whereas others showed good correlation only among patients with marked regression or progression of the disease. Therefore, current data do not indicate that the CEA test is of value in the follow-up of patients with breast cancer.

In patients with cancers of the colon, the CEA levels correlate better with the extent of the tumor, and have prognostic implications. High CEA levels, found in more advanced lesions, imply early recurrence and dissemination. After complete removal of the colonic cancer, preoperatively elevated CEA values usually fall to normal levels in about one month. And progressively rising CEA values usually suggest relapses. However, there is a false-positive rate of 10 to 15 percent, and about 10 to 30 percent of patients with recurrent lesions might have unchanged CEA levels. There are indications that metastatic lesions of the liver and retroperitoneum, often unresectable, are more likely to manifest themselves by rising values of CEA, while other early and localized recurrences are less likely to do so. Based on these experiences, and knowing that Duke A lesions rarely relapse, it appears that CEA tests should only be used as an adjunct to careful clinical follow-up of patients who had curative resection of non-Duke A cancers of the colon. For best cost-effectiveness, an initial CEA test can be obtained at two to three months after resection and repeated at six-month intervals. When a test result differs by more than two standard deviations from a previous one, a repeat test should be obtained.

Serial rising CEA levels in patients with known metastatic gastrointestinal cancer who receive chemotherapy correlate with progression of the disease. Decreases in CEA titers are usually associated with effective therapy, although in some cases the CEA levels might drop preterminally. For patients with nonmeasurable lesions, the CEA test is useful and should be interpreted and considered with other tests and clinical findings.

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Scombroid Poisoning

Report of an Outbreak

PETER A. LERKE, PhD, *and* S. BENSON WERNER, MD, *Berkeley, California*
STEPHEN L. TAYLOR, PhD, *and* LINDA S. GUTHERTZ, MA, *San Francisco*

An outbreak of scombroid poisoning occurred in San Francisco in the fall of 1977. The vehicle was sashimi prepared from spoiled tuna fish. Prompt public health measures prevented further consumption of the implicated food. Laboratory studies showed the presence in the tuna of bacterial species capable of producing large amounts of histamine, a substance strongly implicated in scombroid poisoning. Chemical analysis showed that histamine is very unevenly distributed in the flesh of spoiling tuna, therefore accounting for the sometimes random occurrence of disease among people eating the same food at the same table.

THOUGH RELATIVELY RARE, scombroid poisoning has been known for many years and was first reported in 1799 in Britain.[1] In California, it once was associated primarily with smokehouses and custom canneries that process tuna caught by party boats in the southern part of the state. Reporting, spotty at first, seems to be improving. Consequently, in California, while only ten outbreaks were identified between 1927 (when records were first kept) and 1969, 13 were recorded since 1970.[2] In recent years a number of cases have resulted from the consumption of imported mahimahi (dolphinfish).[2] Since symptoms are dramatic, they seldom fail to attract attention and in the past were often ascribed to fish poisoning (ichthyosarcotoxism) or allergy. However, scombroid poisoning is clearly different from either of these.

In the fall of 1977 a classical outbreak of scombroid poisoning from commercial sources provided the opportunity to study this disease clinically and in the laboratory.

To acquaint readers with this unusual disease, this communication will describe this episode with respect to epidemiology, symptomatology, laboratory findings, etiology and public health control measures and will also discuss certain peculiarities of the disease in the light of new knowledge.

The Outbreak

In accordance with state regulations in California which make mandatory the reporting of all cases of foodborne disease (Section 2500, California Administrative Code, Title 17) and outbreaks of any type (Section 2502), the state's Infectious Disease Section was notified by the San

From the Laboratory for Research in Food Preservation, G. W. Hooper Foundation, University of California, San Francisco (Dr. Lerke), the Infectious Disease Section, California State Department of Health, Berkeley (Dr. Werner), and the Letterman Army Institute of Research, San Francisco (Dr. Taylor and Ms. Guthertz). Dr. Taylor is now with the Food Research Institute, University of Wisconsin, Madison.

Reprint requests to: Peter A. Lerke, PhD, Director, Laboratory for Research in Food Preservation, G. W. Hooper Foundation, University of California, 1950 Sixth Street, Berkeley, CA 94710.

Francisco Department of Public Health of an apparent outbreak of scombroid poisoning associated with several Japanese restaurants in San Francisco.

Phone notification came at 5 PM on Friday, September 16, 1977, with reports of disease in several patrons who dined at three different Japanese restaurants between September 12 and September 15. The San Francisco Department of Public Health had received its information primarily from emergency room physicians who saw many of the patients; and one call was made directly to that department by the owner of one of the restaurants involved.

On investigation 15 cases of scombroid poisoning were found. All of the persons affected had eaten sashimi (raw tuna fish) and became ill 15 to 45 minutes later. In one party of nine people who ate together, only the seven who ate sashimi became ill. In nearly all cases typical symptoms of facial flushing and headache were reported, but there were reports also of rash, swollen tongue, abdominal cramps, nausea, diarrhea, tachycardia and dizziness.

At least 11 of the people felt ill enough to seek medical attention, nine of them at hospital emergency rooms. For most, the illness lasted only a few hours but in one person who ate a large serving of approximately 10 pieces of raw tuna, acute and subacute symptoms lasted three days. As he was an articulate observer, his account is worth recording. He reported dining at one of the three Japanese restaurants on September 13; 45 minutes after eating, dizziness, abdominal discomfort, an unusual sensation ("tightness") in his face, itchy eyes and a dry, swollen feeling in his tongue developed. Abdominal discomfort steadily worsened and was followed by "violent illness" and "enormous" amount of diarrhea which began at midnight, two and a half hours after dinner. Diarrhea continued for two and a half hours, abdominal pain persisted through the night, and flatulence and weakness were present in the morning. Intermittent diarrhea, weakness and depression were experienced for the next three days; not until a full week had elapsed did this person feel normal again.

The same observer reported that of the three people who ate sashimi with him that evening, only he became violently ill, while his wife had no adverse effects whatever and a third person experienced only moderate abdominal discomfort. Five weeks previously, however, his wife became ill while he remained well after eating sashimi at the same restaurant. As we will discuss later, these events probably relate to uneven contamination of the raw tuna with agents causing scombroid poisoning.

Source and History of the Fish

Information provided by the Los Angeles office of the Food and Drug Section, California Department of Health, disclosed that the fish was part of a 78 ton catch of yellowfin tuna taken off the coast of Mexico by a San Diego vessel. In all, 76 tons of the fish were frozen at sea in brine for canning, and 2 tons (presumably the choicer fish) were stored separately, whether on ice or in a cooler could not be determined, but in any event were not frozen in brine. These fish were destined for sale as sashimi. The 76 tons of brine frozen fish were canned and distributed under a national label, and no complaints were received about that product. The two tons of "fresh" (meaning nonfrozen) fish were picked up on Friday, September 9 at the San Diego dock, when the boat returned to port, by the refrigerated truck of the Los Angeles county wholesaler who reported that his truck did not fail to keep the temperature below 5°F. That wholesaling company cleaned and processed the fish on its San Pedro premises and reported a normal weight loss of 25 percent, leaving 3,000 pounds of salable merchandise. A San Francisco trucker picked up more than 2,000 pounds of that fish on September 9 and delivered it to four distributors (A, B, C, D) in the San Francisco Bay area. There was no indication that his refrigeration equipment was not working properly.

Investigation showed that two of the restaurants were supplied "fresh" tuna by one San Francisco fish distributor (distributor A) and the third restaurant was supplied by another San Francisco fish distributor (distributor B). It is pertinent that one of the three restaurants cited above had returned 545 pounds of that shipment back to distributor A before there were any reports of illness, simply because the fish was malodorous and decomposed. Distributor A then returned all of that fish to its wholesaler in Los Angeles County for credit. Quite independently, so did distributors B and C return fish later for the same reason. No cases of illness, however, were ever associated with fish distributed by distributor C or D.

Distributor D never returned any fish, perhaps because of that company's smaller volume of business; it bought the least of all four companies, only 280 pounds.

Of all the fish returned to the San Pedro wholesaler, only 75 pounds were discarded as spoiled while the rest was sold to a Terminal Island plant for canning.

Public Health Control Measures

In view of the potential hazard represented by the spoiled fish, the State's Infectious Disease Section requested on September 16 that an embargo be placed on the entire lot. This was done by the State Food and Drug Section and the Los Angeles County Health Department before any of the fish, raw or that which was later canned, could be sold. Samples of both the raw and canned product were analyzed at the University of California's Laboratory for Research in Food Preservation and, on the basis of the results obtained, the entire lot was destroyed.

Etiology of Scombroid Poisoning

It is important to differentiate scombroid poisoning from both so-called fish poisoning and fish allergy. Fish poisoning or ichthyosarcotoxism may result from the ingestion of certain species, mostly from tropical regions, whose flesh contains powerful toxins, although there is no evidence to indicate that so-called poisonous species are poisonous all the time or in every locality. In any case, the state of freshness of the fish has no relation to the ability of those fish to cause illness, and the symptoms produced are different from those of scombroid poisoning and much more severe. Examples of ichthyosarcotoxism are ciguatera and puffer fish poisoning.

With regard to possible allergy, the distinction is not quite so clear-cut because one of the substances that mediate allergic reactions, histamine, also seems to be involved in scombroid poisoning, per the following observations:

- The symptoms of scombroid poisoning closely resemble those of histamine effect.
- Administration of antihistamines relieves the symptoms of scombroid poisoning.
- In every incident of scombroid poisoning studied, high levels of histamine have been found in the implicated food.

Despite the seemingly crucial role of histamine, scombroid poisoning does not appear to be an allergic reaction. This is evidenced by (1) group outbreaks that may show practically 100 percent morbidity, whereas allergy to fish protein is a relatively rare occurrence; (2) observations that people who habitually eat raw fish only occasionally have signs of scombroid poisoning, and (3) the fact that histamine is present in the fish itself rather than being produced by the host as in allergy.

If histamine is the culprit, where does it come from? Because the histamine content of fresh, nondecomposed fish is well below 1 mg per dl, it becomes necessary to explain the mechanism whereby levels approaching 1,000 mg per 100 grams of flesh (1 percent) can be found in fish implicated in scombroid poisoning.

The name scombroid derives from the family Scombridae which includes mackerels, tunas and bonitos. It is this group that has caused, over the years, most scombroid poisonings. But this family does not have exclusive rights: the dolphinfish (Coryphaena hippurus) has also caused a number of outbreaks but is not at all related to the mackerel group. Even foods other than fish have caused scombroid poisoning and there is one recent report implicating a fermented cheese.[3]

It has been found, however, that all fish that cause scombroid poisoning have one thing in common: a high level of *free* histidine in their muscle tissues. All fish have this amino acid in their protein. Being part of a chain, both of the reactive end-groups of the molecule are relatively inaccessible to bacterial enzymes during spoilage. In scombroid fish and in mahimahi, however, histidine is not only present in protein but also exists, in large amounts, as the free amino acid and so is easily available for reaction.

Histidine is converted to histamine by decarboxylation. This occurs easily when the fish undergoes spoilage, because a number of bacterial types are able to produce decarboxylase.

In view of the above, it is natural that histamine levels should be the first thing studied in analyzing samples of food implicated in scombroid poisoning. Nevertheless, while we know that histamine is produced during spoilage, the actual mechanism of scombroid poisoning remains a mystery because according to current knowledge, histamine is not active when taken by mouth.[4,5] Furthermore, as a result of bacterial activity, our intestinal contents have more than enough hista-

mine to make us ill if that histamine were absorbed into the bloodstream.[4,6]

There are several possible explanations, all centering on still unidentified substances (such as "saurine"[7]) that may be formed during protein breakdown and be present in spoiled fish along with histamine. The presence of high histamine levels may merely represent a marker for the real disease-producing agent that may be there at the same time. Alternately, it is conceivable that some of these substances can facilitate the penetration of histamine through the gut or that they can somehow trigger the release of the body's own histamine, although the latter possibility appears unlikely in view of some experimental work with rats (James L. Lenney, Department of Pharmacology, University of Hawaii, oral report, Nov 22, 1977, personal communication).

Laboratory Results

Histamine levels were determined by two different methods. The University of California, San Francisco, laboratory used the fluorometric procedure of Lerke and Bell,[8] which is comparable to the current Association of Official Analytical Chemists (AOAC) procedure based on the same principle.[9] Letterman Army Institute of Research used the slightly different fluorometric procedure of Taylor and co-workers.[10]

Three separate sets of sample material were obtained. The first was collected on September 16 at one of the restaurants by the San Francisco Health Department and was split between the University of California Food Preservation Laboratory and Letterman Army Institute of Research. This sample consisted of a small amount of raw tuna scraps collected from the kitchen.

The flesh of this initial sample had a definite odor of decomposition. Six areas were sampled from the portion provided to the Food Preservation Laboratory. Analysis for histamine gave values of 565, 160, 600, 594, 516 and 325 mg per dl. A single test of the portion provided to Letterman Army Institute of Research gave a histamine content of 919 mg per dl.

The remainder of the sample at the Letterman Army Institute of Research was subjected to bacteriological analysis. The aerobic plate count (APC)[11] and presumptive coliform plate count[11] were 7.0×10^7 and 8.3×10^5 organisms per gram, respectively. The method of Guthertz and associates[12] was used for the isolation and identification of aerobic Gram-negative organisms. Two biotypes each of Proteus vulgaris and Klebsiella pneumoniae were isolated along with single biotypes of Citrobacter freundii, Enterobacter agglomerans, Hafnia alvei, Acinetobacter calcoaceticus, Proteus rettgeri and Enterobacter cloacae. These bacterial strains were examined for their ability to produce histamine in a tuna fish infusion broth (TFIB) prepared as follows: fresh tuna muscle was homogenized with 2 volumes (w/v) of water, steamed at 100°C for one hour, filtered through paper, supplemented with 1 percent glucose, and sterilized at 120°C for 15 minutes. Then, 70 ml of TFIB was inoculated with 2 ml of an 18-hour trypticase-soy broth-histidine culture of each of the isolated organisms, and incubated for seven hours in a shaking incubator at 32°C. The growth and net histamine production by these bacterial strains after the seven hour incubation in TFIB are shown in Table 1.

TABLE 1.—*Production of Histamine in Tuna Fish Infusion Broth by Various Bacterial Species*

Species	*Log Increase in APC*	*Net Histamine Production (nmoles/ml)*
Proteus vulgaris biotype 1	1.89	<1
Proteus vulgaris biotype 2	1.74	23
Klebsiella pneumoniae biotype 1	1.74	19,900
Klebisella pneumoniae biotype 2	1.44	<1
Citrobacter freundii	2.09	<1
Enterobacter agglomerans	1.65	31
Hafnia alvei	1.55	5
Acinetobacter calcoaceticus	1.79	<1
Proteus rettgeri	1.88	<1
Enterobacter cloacae	1.75	<1

APC = aerobic plate count

The results indicate that one particular strain of K. pneumoniae could have been responsible for the high levels of histamine encountered in the tuna. Bacteriological studies of material from previous outbreaks had shown Proteus morganii to be the most active histamine producer[13,14] and, to our knowledge, had never implicated K. pneumoniae.

A second set of specimens was collected by the State Food and Drug Section at the San Pedro wholesaling company, after the fish had been returned there from San Francisco, and these specimens were examined at the university laboratory. One sample consisted of a half cross section of a fish, approximately 25 cm by 15 cm, and 15 cm thick, taken at the level of the gut cavity. There were two other smaller pieces whose average histamine content was determined

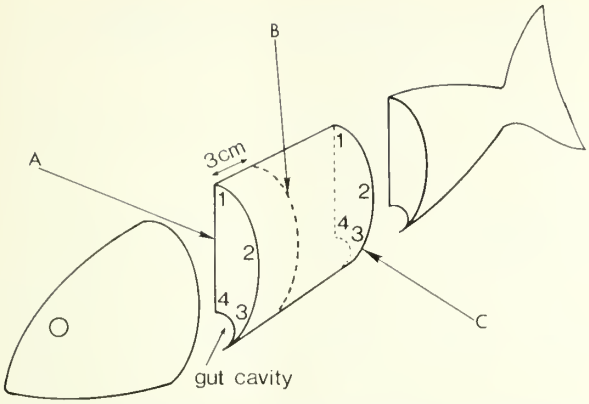

Figure 1.—Schematic representation of tuna fish section from which samples were taken for analysis of histamine (see text). Results are shown in Table 2.

to be 821 and 716 mg per dl, respectively. Of special interest, however, was the large piece since it allowed us to study the distribution of histamine in the fish flesh.

Three specimens, approximately 10 grams each, were taken along the periphery of the fish, about 2 cm under the skin starting at the dorsal fin and proceeding ventrally (Figure 1). A fourth specimen was taken next to the gut cavity. This sampling pattern was carried out in three planes: the anterior surface (A), a plane 3 cm caudad to it (B) and the posterior surface of the section (C). In each plane the sampling areas were spaced about 8 cm from each other. In the case of plane B a double amount of flesh was cut out and split into two pieces which were analyzed separately. This was done to assess the variability in histamine levels over very small distances. Consequently, two values are shown in the corresponding column of Table 2.

In that the maximum analytical error of the method is 10 percent, it can be concluded from these results that the distribution of histamine in spoiling tuna is quite uneven, varying more than fourfold over a distance of 3 cm (location 4, columns A and B) and almost threefold in contiguous areas (location 1, column B). Furthermore, the concentration of histamine seems to be higher near the gut cavity.

The final set of samples received by the university laboratory consisted of product canned from the same lot of tuna. Of 24 cans examined, half had histamine values above 10 mg per dl, ranging up to 113. Accordingly, and as indicated previously, the lot was destroyed.

TABLE 2.—*Mg per dl of Histamine in Various Anatomical Locations of a Spoiled Tuna Fish*

	Plane		
*Location**	*A*	*B*	*C*
1	48	15, 43	15
2	4	4.0, 5.7	7
3	26	73, 139	11
4	124	656, 659	314

*See Figure 1.

Discussion

Several factors are important to our understanding of scombroid poisoning. First, it is a consequence of spoilage that occurs at fairly high temperatures. For many years a close relationship has been recognized between tuna being held at elevated temperatures, such as on decks of party boats in Southern California, and episodes of scombroid poisoning. Conversely, tuna that has been allowed to spoil at temperatures below 10°C has never, to our knowledge, been implicated in scombroid poisoning and has not contained histamine levels above 25 mg per dl.

Few bacteriologic studies, of the kind presented in this paper, are available in the literature. However, the types of bacteria that have been found in connection with this type of spoilage belong almost exclusively to the enteric group, where the optimum growth temperature is around 37°C (98°F) with a maximum at about 43°C (109°F). This is compatible with recently obtained preliminary data showing that under controlled spoilage conditions, the highest levels of histamine are obtained in tuna held between 95 and 100°F (Helmer A. Frank, Department of Food Science, University of Hawaii, oral report, Aug 14, 1978, personal communication). Those very conditions are commonly encountered during commercial tuna fishing operations.

While tuna seining is usually done in tropical waters at about 80°F, the body temperatures of these metabolically active fish may be as much as 15° higher. As soon as the purse is tightened, the fish die of asphyxiation and decomposition begins.

Normally the fish are transferred into cold brine and frozen before any gross damage can occur but any factor that prevents or delays cooling will notably increase the likelihood of histamine production. Examples are mechanical or refrigeration breakdowns, unusually large fish and overloading of storage wells.

In the present outbreak we have no evidence of undue delays in bringing the fish on board but we do know that the fish set aside for the "raw fish" trade were large and that they were not placed in the cooling brine. Whether they were put on ice or in a refrigerator, the rate of cooling must necessarily have been considerably slower, affording ample opportunity for bacterial proliferation during the first 18 hours or so.

Another remarkable aspect was that some of the fish that caused illness, and which was later found to contain very high levels of histamine, was judged acceptable by several persons who would have been expected to be discriminating, namely people in charge of sashimi preparation in at least one Japanese restaurant, as well as their patrons. Likewise, the large section of raw fish examined by one of us (P.A.L.) had only a very mild "off-odor," yet a high level of histamine.

Similar observations are well documented in the literature[15,16] and are consistent with our knowledge about the bacteriology of fish spoilage. Specifically, histamine-producing bacteria do not seem to be true spoilage bacteria in the sense that they do not necessarily give rise to the offensive odors that we associate with spoilage. While the two types may coexist in any given fish environment, this is not always the case; there are numerous cases on record at the university laboratory of spoiled tuna low in histamine and, conversely, of seemingly acceptable fish with very high histamine levels.

Also important is the observation that histamine levels vary tremendously over very short distances in the same cut of flesh. This explains why not everyone sharing the same poorly-preserved fish need suffer illness and also why in the investigation of consumer complaints, it is important to obtain for analysis a portion of the food that was actually eaten as well as that which is available in the restaurant's refrigerator.

The episode just described illustrates the importance of prompt reporting by physicians of any cases of food poisoning of which they may become aware, since it enables public health authorities to launch immediate control measures and thereby prevent exposure of additional persons. Moreover, in most states such reporting is required by regulations for just that purpose. Indeed, failure to report a reportable disease was among the charges in the disciplinary action taken by the Board of Medical Quality Assurance in 1978 against a Bay Area physician.

For further information on scombroid poisoning the reader is referred to the excellent review by Hudson and Brown.[17]

Addendum

At the 1978 annual meeting of the American Society for Microbiology, Drs. Donald A. Corlett, Mark B. Jeffrey and Charles F. Niven, Jr., of the Del Monte Research Center in Walnut Creek, California, reported on the isolation of strains of Klebsiella pneumoniae that were able to produce high levels of histamine from raw mackerel gut and from mahi-mahi fillets.

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The Obesity-Hypoventilation Syndrome

EDWARD J. MORGAN, MD, PhD, *and* CLIFFORD W. ZWILLICH, MD, *Denver*

The triad of obesity, hypoventilation and inordinate hypersomnolence characterizes the obesity-hypoventilation syndrome. The reasons for daytime hypoventilation appear related to decreased chemical drives to breathe combined with the added physical impediment of extreme obesity. When the physiology of sleep was investigated in patients with this syndrome, intermittent nocturnal obstructive apneas were documented that produced blood gas abnormalities, arrhythmias and serious elevations of both pulmonary and systemic pressures. The obstructive apneas are due to intermittent loss of muscle tone of the tongue resulting in its prolapse against the posterior pharynx. The special importance of the obesity-hypoventilation syndrome lies in its being an example of a disorder of sleep and breathing that can appear in widely different clinical settings. Therapeutic measures include weight loss, progestational agents or permanent tracheostomy.

THE OBESITY-HYPOVENTILATION SYNDROME (OHS) is an uncommon illness characterized by obesity, hypoventilation and often irresistible hypersomnolence. It might have remained only a grotesque curiosity were it not for interest in its fascinating pathophysiology, involving disorders of both sleep and the control of breathing.

When investigators examined the physiology of sleep in OHS, an unexpected series of life-threatening events was documented. Even such dissimilar examples as sleep at high altitude[1] and respiratory control in some patients with chronic obstructive lung disease[2] share a mechanism with OHS. Therefore, the reader should realize that the pathophysiology of the OHS is similar to that found in more common medical disorders. This review describes in detail the physiology of OHS, discusses its interrelationships with other disorders and provides a basis for therapy.

From the Cardiovascular Pulmonary Research Laboratory and Division of Pulmonary Sciences, Department of Medicine, University of Colorado Medical Center, Denver.

Dr. Zwillich is a recipient of NIH Research Career Development Award (HL 00225).

Reprint requests to: Clifford W. Zwillich, MD, CVP Research Laboratory, B-133, University of Colorado Medical Center, 4200 E. Ninth Avenue, Denver, CO 80262.

Background

The OHS has been recognized for over a hundred years. Early investigators knew that a correlation existed between obesity and cardiopulmonary problems. In the past it has been called obesity heart disease[3] and the postural syndrome related to obesity and cardiorespiratory failure.[4] In 1956 Burwell, Robin and colleagues coined the term Pickwickian syndrome.[5] We prefer the name obesity-hypoventilation syndrome (OHS), which emphasizes the abnormal ventilation found in these patients.

Pathophysiology

Hypoventilation with an elevated arterial partial pressure of carbon dioxide (P_{CO_2}) is the central pathophysiologic disturbance in patients

with OHS. The subsequent hypercapnia, acidemia and hypoxemia cause a rise in the mean pulmonary artery pressure with resultant right heart failure. Hypoventilation is most severe during sleep, and may result in severe transient systemic hypertension which places a significant burden on left ventricular ejection. Left ventricular failure then ensues which further compromises the patient's condition.[6] Erythrocytosis commonly occurs with a hematocrit over 60 percent.[7]

Mechanical Factors

Early investigators attempted to blame obesity alone as the major cause of hypoventilation.[8-10] Several lines of evidence show that this is not the case. First, only a minority of obese patients have significant hypoventilation[8-12] and there is no correlation between body weight and arterial carbon dioxide pressure (P_{CO_2}) in obese patients.[13] Second, in patients with OHS, arterial blood gas values easily return to normal with voluntary hyperventilation, indicating that mechanical factors are not critically limiting the patients' ability to ventilate normally.[14,15] Third, one need not be massively obese to hypoventilate, which suggests that other factors are also at work.[11,16-18] Last, elastic loading of respiration in normal persons (used to simulate obesity) is not associated with hypoventilation.[19] Although patients with OHS have restrictive abnormalities of lung function that are more severe than those of patients with simple obesity,[20] this alone appears insufficient as a cause of hypoventilation. Moderate weight reduction in patients with OHS leads to marked improvement in vital capacity, lung compliance, arterial blood gas values, and clinical symptoms.[20] This suggests that either the absolute weight or the distribution of obesity which is usually truncal in patients with OHS may be important factors in the pathogenesis. Weight loss may result in a critical decrease in the work of breathing.[21] Although the role of excess weight in patients with OHS is only a cofactor, it undoubtedly plays a synergistic role. There is no doubt, however, that weight reduction is effective in treating patients with OHS.[5,8,18,20,22]

The hypoxemia associated with OHS is frequently more severe than what would be expected on the basis of the degree of hypoventilation.[15] This may be explained by ventilation/perfusion mismatch with decreased basilar ventilation.[23]

Factors That Control Respiration

Mechanical factors alone do not provide an explanation for hypoventilation, as was emphasized by Bedell, Wilson and Seebohm in 1958 when they showed that most obese persons do not hypoventilate unless an insult such as pneumonia or myxedema is added.[8] Because obesity alone does not explain the hypoventilation of patients with OHS, studies have been done to evaluate the homeostatic mechanisms controlling arterial P_{CO_2} and oxygen pressure (P_{O_2}) in this syndrome.

Arterial P_{CO_2} is closely controlled in healthy persons within a narrow range. Increases of P_{CO_2} are met with a steep linear ventilatory response averaging at least a three-fold increase in minute ventilation per rise in P_{CO_2} of 10 mm of mercury.[24]

The normal increase in ventilation stimulated by inhalation of carbon dioxide (CO_2) is blunted in patients with OHS and not in patients with comparable simple obesity.[25,26] Decreased responses to CO_2 have also been shown in nonobese patients who hypoventilate,[17] and in patients with idiopathic hypoventilation (Ondine's curse).[16,27] In patients with OHS, weight loss usually improves the hypercapnic ventilatory response, suggesting that the decreased response may be the result of mechanical consequences of obesity and not the primary cause of hypoventilation.[5,28] Whether a blunted hypercapnic response is a primary pathogenetic mechanism of the syndrome or is only a secondary finding is unresolved.

Similarly, a blunted hypoxic ventilatory response is a common finding in these patients[25,29] and is reduced to approximately 20 percent of normal values.[25] The carotid body is the major detector of decreased levels of arterial oxygen tension,[30] and minute ventilation rises exponentially when P_{O_2} falls below 50 to 60 mm of mercury.[31] Chronic hypoxemia can blunt the hypoxic ventilatory response, as seen in residents of high altitude[32] and in patients with cyanotic congenital heart disease.[33] Since weight loss may not improve the ventilatory response to hypoxia,[34] a blunted hypoxic response may be a primary rather than a secondary feature of the syndrome. Blunting of the response due to chronic hypoxemia is an unlikely possibility, because it takes over 25 years of hypoxemia before a reduced hypoxic drive is seen in persons living at high altitude.[32] Hence, the reason for this blunted hypoxic re-

sponse in OHS is unknown. There is evidence to suggest that a decreased hypoxic response may be genetically mediated. Studies in endurance athletes,[35] in patients with chronic obstructive lung disease with hypoventilation,[2] and in twins[36] all suggest that there is a significant familial predisposition for the hypoxic ventilatory response. It may be that in obese patients who are genetically preselected for abnormalities in ventilatory drive, OHS develops.

An enticing theory about obesity and decreased chemical drives to breathe is alluded to in a report of an obese child with hypoventilation and evidence of hypothalamic injury. The patient was found to have a voracious appetite, diabetes insipidus, lethargy and cyanosis.[37] However, this possible central nervous system abnormality has not proved to be universal in patients with OHS, as post-mortem studies on these patients typically failed to show any consistent central nervous system abnormalities.

Sleep Studies

Hypersomnolence is a severe and striking part of the OHS. Joe in Dickens' *The Posthumous Papers of the Pickwick Club* fell asleep while knocking on a door.[38] Burwell's patient realized that he needed medical help when he fell asleep holding a full house during a poker game.[5] Patients have also been known to fall asleep while driving a car.

The reasons for this hypersomnolence have only recently been understood. Because acute elevations of arterial P_{CO_2} values produce disorientation, lethargy, and coma, it was thought that somnolence was related to carbon dioxide narcosis. However, somnolence does not correlate with an elevated P_{CO_2}.[39,40] Indeed, somnolence usually precedes any rise in P_{CO_2} in patients who are awake.

Patients with an acutely elevated P_{CO_2} become disoriented, obtunded and finally comatose and unarousable. Patients with OHS display a different pattern, with irresistible somnolence yielding to a deep sleep from which the patient can be aroused.[41]

Critical studies which ultimately led to the understanding of the mechanism of sleep-wakefulness disturbances in OHS were those of Gastaut, Tassinari and Duron, who documented dramatic cyclic breathing pauses or apneas in certain patients with OHS.[39] During such pauses airflow ceased but respiratory effort, measured as intrathoracic pressure swings, continued. These are termed obstructive, or peripheral apneas. This intermittent upper airway obstruction was accompanied by significant hypercapnia and hypoxemia.[39] No apneas were detected during wakefulness. This observation has been extended to

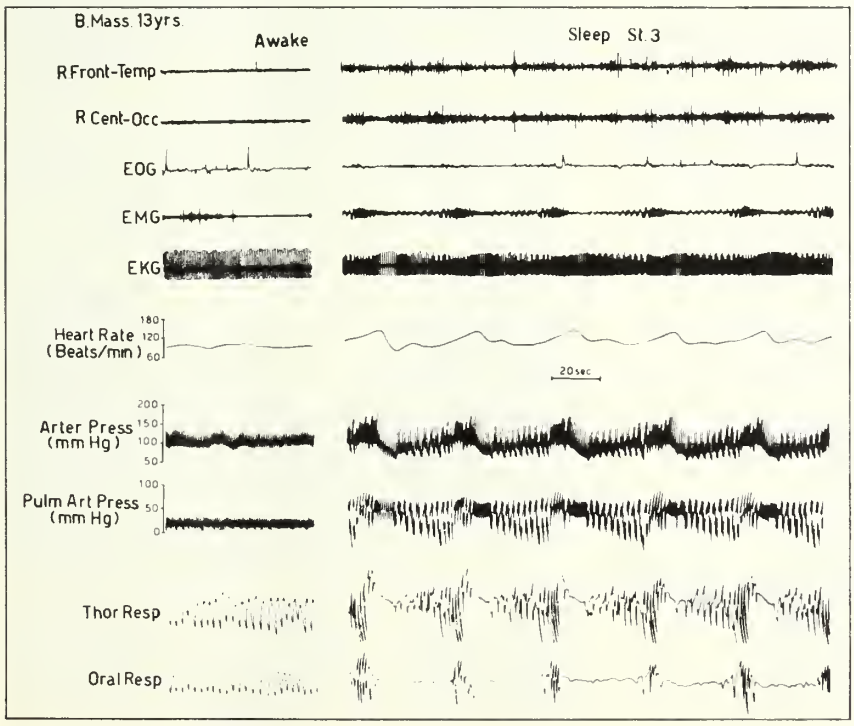

Figure 1.—Nocturnal sleep record of a patient with OHS and obstructive sleep apnea. Oral respiration has stopped although thoracic excursions of increasing effort continue. Pulmonary and systemic hypertension are illustrated along with the cyclic bradycardia often found in OHS. (From Coccagna et al[6]).

large numbers of patients with OHS.[6,18,22,39-44] The collected evidence shows that soon after the onset of sleep, apnea caused by upper airways obstruction ensues, accompanied by continued but ineffective diaphragmatic attempts at ventilation. Within thirty seconds to two minutes, the arterial P_{O_2} falls to values often as low as 20 to 30 mm of mercury and the arterial P_{CO_2} rises to a range of 60 mm of mercury. During this time both pulmonary and systemic hypertension[41,42] occur, probably caused by the combined effects of hypoxia, hypercapnia and reflex sympathetic discharge. Both right and left ventricular failure may ensue. A sleep recording in a patient with OHS in which some of these findings are documented is shown in Figure 1.

The cause and site of the obstructive apnea are debatable. Cinefluoroscopy and fiberoptic observation have shown that during sleep the tongue may fall backwards into the posterior pharynx. The obstruction appears to be in the posterior pharynx at the base of the tongue. A clue to the cause of the obstruction came from electromyographic (EMG) studies of several muscles whose function is to insure a patent airway. These muscles have a tonic discharge while an individual is upright that normally intensifies while supine in order to insure airway patency. For example, the genioglossus is a large muscle located at the base of the tongue, and active contraction of this muscle appears to be required to maintain a patent airway. Recent electromyographic studies of this muscle in patients with OHS have shown that suboptimal EMG activity may occur, thus allowing the base of the tongue to remain prolapsed against the posterior pharynx.[45] The possible site of obstruction is shown in Figure 2. Bypassing the intermittent obstruction with a nasopharyngeal tube has reversed the symptoms of OHS.[22] In obese patients with a florid nocturnal obstructive sleep apnea syndrome tracheostomy has returned arterial blood gas values to normal and has dramatically reversed subjective symptoms, hypoxemia-induced erythrocytosis, pulmonary hypertension and heart failure.[40,41] Symptoms return and signs of right ventricular failure and erythrocytosis recur up to a year later if the tracheostomy tube is occluded.[22] Moderate weight loss has a beneficial but incomplete effect on obstructive apnea, supporting the view that the *distribution* of fat may be important.[18]

At the end of the apnea the electroencephalogram shows that the sleep stage lightens, frequently to full awakening, and ventilation resumes with a snorting gasp as the obstruction is broken.[43] The P_{O_2} and P_{CO_2} values return toward normal, only to enter a new cycle a few minutes later. Such patients may sleep less than 30 seconds at a time,[39] may actually be awakened over 30 times an hour and may spend less than two hours in effective sleep per night.[39] Each period of apnea lasts from 15 to 60 seconds.[43] In the morning the patient awakes disoriented, groggy and usually with no knowledge of the recent struggle. Only the patient's spouse may have noted the snoring, twitching, periodic breathing and spells of cyanosis.

The sleep deprivation sustained by these patients can be subtle, and often only psychiatric disturbances are evident. Personality disorders including paranoia, agitated depression and hos-

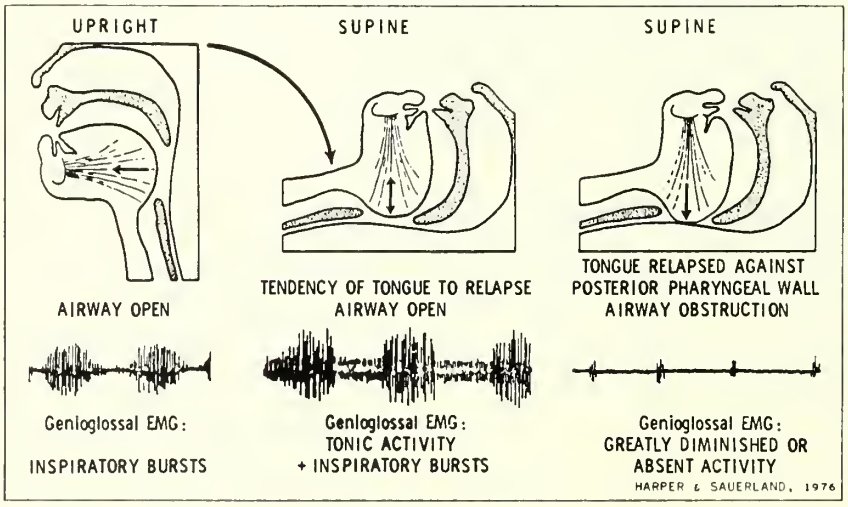

Figure 2.—Median sections through the region of the pharynx showing the probable site of obstruction. Normally, EMG activity increases in the supine position in an attempt to insure a patent airway. Obstruction appears to occur when supine EMG activity is greatly diminished. (Reproduced by permission from Harper RM, Sauerland EK: The role of the tongue in sleep apnea, **In** Guilleminault C, Dement WC (Eds): Sleep Apnea Syndromes. New York, Alan R. Liss Inc, 1978, p 225). EMG = electromyogram.

tility have been shown to occur frequently and can be abolished with treatment.[44] Life-threatening accidents, job loss, and familial alienation may all be related to hypersomnolence.

Life-threatening arrhythmias occurring during obstructive apneas have been noted in these patients during sleep.[6] Although tachyarrhythmias, including ventricular tachycardia, occur, severe cyclic bradyarrhythmias appear to be more common (Figure 1). It is likely that this cyclic bradycardia is vagally mediated because it responds to atropine. Cyclic bradycardia is suggestive of OHS, and affords a convenient means to confirm the diagnosis by use of a Holter monitor. The occurrence of sudden death in these patients may be related to such arrhythmias.[46]

Clinical Presentation and Diagnosis

The gross obesity and hypersomnolence of the patient with classic OHS provide an unforgettable and unfortunate picture (Figure 3). However, the diagnosis in mild variants of the syndrome is more difficult. In fact such patients are frequently mislabeled and treated for pure erythrocytosis in a hematology clinic, depression or paranoia in a psychiatric unit, idiopathic congestive heart failure in a cardiology clinic, or atypical chronic obstructive pulmonary disease with cor pulmonale in a general medical clinic.

Figure 3.—A woman patient in whom the classic obesity hypoventilation syndrome is seen. Irresistible hypersomnolence, cor pulmonale and polycythemia were present. Hypoventilation was severe (arterial carbon dioxide tension [$PaCO_2$] = 68 mm of mercury) but was normal ($PaCO_2$ = 37 mm of mercury) after two minutes of voluntary hyperventilation.

It has been found at the Stanford University sleep clinic that over 15 percent of patients presenting with insomnia have sleep apnea and physiologic disturbances similar to those of OHS.[47]

Studies of patients with OHS show a five-year mortality rate of over 50 percent due to causes including pulmonary emboli, respiratory failure and sudden death.[46,48]

Suspicion followed by clinical observation play a major role in diagnosing OHS. Disturbed sleep, morning headache, idiopathic heart failure or erythrocytosis are clues. Because of an almost amnesic state sometimes produced by sleep deprivation, subjective complaints may be absent. Frequently, as mentioned earlier, only the patient's spouse will recall the snoring, spells of apnea or episodes of cyanosis.

Observing the patient during sleep will often provide convincing proof. Cessation of airflow at the mouth and nose while vigorous abortive attempts at breathing continue, is diagnostic. Reliance on arterial blood gas samples taken during wakefulness to detect hypoventilation is fraught with error. Often these patients hypoventilate only while supine or asleep and when obstruction occurs.

Patients in whom the classic features of OHS are seen should not be hard to diagnose (see Table 1). However, in more subtle cases, nocturnal monitoring is very helpful.

The fiberoptic ear oximeter may be used to document nocturnal oxygen desaturation.[49] If desaturation occurs during an episode of obstructive apnea that is corrected by a nasopharyngeal tube, the desaturation is probably due to an obstructive apnea. If, however, saturation falls without obvious diaphragmatic excursions, the apneas may be centrally mediated and not ob-

TABLE 1—*Features of the Obesity-Hypoventilation Syndrome*

Primary	*Secondary*
Obesity	Polycythemia
Hypoventilation	Cyanosis
Hypersomnolence	Periodic respiration
	Psychiatric disturbances
	Snoring
	Twitching
	Right ventricular failure
	Morning headache

structive. This is an important point regarding the choice of therapy.

Cardiac monitoring is also a helpful way to evaluate such patients. The cyclic episodes of bradycardia often seen in these patients may be the first clue that obstruction is occurring, and reviewing a 24 hour Holter recording may document arrhythmias suggestive of apneas occurring at night.

Documenting nocturnal obstructive apneas and, if possible, showing improvement after several nights sleep with a nasopharyngeal tube in place should be required before any invasive form of therapy such as tracheostomy is attempted. Because some patients may require life-long tracheostomy, questionable cases should be referred to an experienced sleep laboratory for specific diagnosis.

Treatment

It may be that obstructive apneas and other events during sleep represent the most pressing indications for treatment. Life-threatening forms of obstructive OHS, particularly those associated with serious bradyarrhythmias and tachyarrhythmias, and profound oxygen desaturation, require immediate endotracheal intubation followed by elective tracheostomy. In less serious cases, weight reduction and low flow oxygen breathing benefit many patients.

Weight reduction is clearly the first mode of therapy to be attempted and ventilation can be expected to improve with as little as a 5 to 10 percent loss of body weight. After such a weight loss, obstructive apneas, hypercapnia, pulmonary hypertension and somnolence often lessen.[18,43] Unfortunately, weight reduction is often not possible in this group of patients, and long-term success is unlikely. When the attempt at losing weight fails and the degree of hypoxemia is severe, low flow oxygen breathing should be administered at night. Increasing nocturnal arterial blood oxygen saturation to about 90 percent should not produce severe CO_2 retention and will often result in substantial reversal of cor pulmonale and erythrocytosis, although the obstructive sleep apneas may continue.

Another approach to therapy is the use of progestational agents. Progesterone is known to be responsible for hyperventilation in pregnancy and the luteal phase of the menstrual cycle.[50,51] It stimulates alveolar ventilation with a reduction in P_{CO_2} values and increases the ventilatory response to hypercarbia and hypoxia in normal persons.[52] In patients with OHS, medroxyprogesterone acetate improves ventilation and reduces heart failure and erythrocytosis,[14,53] although obstructive apneas may continue.

TABLE 2.—*Factors Known to Exacerbate Hypoventilation and Hypoxemia*

Intrinsic lung diseases	Thyroid insufficiency
Altitude	Neuromuscular disease
Sedative-hypnotic drugs	Mechanical restriction
Respiratory tract infections	Reactive airways diseases
Congestive heart failure	Neurological diseases
Pulmonary emboli	

Patients with the obstructive form of OHS have dramatically responded to tracheostomy. Within days, florid heart failure, hypersomnolence and paranoid ideations have disappeared. Occlusion of the tracheostomy tube at any time thereafter has caused the syndrome to reoccur.[22,40,41] Indications for tracheostomy include severe asphyxia, sleep deprivation due to nocturnal arousals and major arrhythmias. Alternatively, a nasopharyngeal tube has been used to establish an airway each night, but patient acceptance of this has not been good.

Every effort must be made to exclude or minimize other causes of hypoventilation or hypoxemia (see Table 2). These causes must be evaluated and corrected before the patient can be assumed to have the syndrome. In many cases, the patient will improve after elimination of a secondary cause.

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Specialty Conference

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Participants

JAMES D. CONNOR, MD
ROGER A. WILLIAMS, MD
MURIEL A. THOMPSON, DrPH
MICHELE GINSBERG, MD
SANDRA DALEY, MD

From the Department of Pediatrics, University of California Medical Center, San Diego; the Department of Pathology, Childrens Hospital and Health Center, San Diego, and the Department of Public Health, County of San Diego

Plague in San Diego

JAMES D. CONNOR, MD:* *Bubonic plague occurs most frequently in children and adolescents. In some areas of California and the Southwest, insect vectors and wild rodents together provide endemic foci for plague, from which there is occasional distribution to persons traveling to those areas. The clinical syndrome of bubonic plague fits very well within a group of syndromes of febrile origin in pediatrics; therefore, the usual clinical presentation of plague is difficult to recognize unless the index of clinical suspicion is high. The clinical syndrome and the bacterial infection are treatable by readily available means. Diagnostic laboratory procedures are available in San Diego county; the diagnosis is easily made once the necessity of making a diagnosis is recognized. The bacterial infection and clinical syndrome yield to treatment quickly with a low mortality; if the infection is not recognized, the mortality is very high and the syndrome time is very short. For these reasons we felt that we as pediatricians should become acquainted with plague.*[1-3] *The recent plague death in the county is the only recorded case of the plague in San Diego. This conference discusses the various aspects of plague in children: pathogenesis, pathology, clinical diagnosis, bacteriologic diagnosis and treatment. Doctor Daley will present the case for us.*

SANDRA DALEY, MD:† The patient is a white girl, aged 3 years and 9 months, who was in good health until five days before admission to hospital. While on vacation with her family at Lake Tahoe, she became ill, with fever, delirium and vomiting. Her parents administered aspirin, but the child was unable to keep any medicine down. The fever persisted; at the height of fever, brief jerky and kicking movements, which lasted a few seconds, were noted. She was lucid, and her parents did not notice any rolling back of the eyes. Because of her illness, the family returned to San Diego. On the evening of their return, she was seen in the emergency room of a local hospital, where it was noted that she had a temperature of 38.9°C (102°F), a heart murmur and tonsillitis. Penicillin was prescribed at 125 mg four times a day and an aspirin suppository was given, which promptly reduced her fever. The following day, although she ate poorly and

*Professor of Pediatrics.

Dr Thomas Quan of the Center for Disease Control Plague Laboratory in Fort Collins, Colorado, shared slides that allowed us to compose tables of biochemical reactions. He also supplied slides showing phage test results and fluorescent antibody stain reaction, along with specific conjugate and phage test strips that made identification of the isolate possible.

Reprint requests to: James D. Connor, MD, Head, Pediatric Infectious Diseases, M-009, University of California, San Diego, La Jolla, CA 92093.

†Pediatric Resident.

vomited a dose of aspirin, her parents felt she was somewhat improved. Two days before admission to hospital she was notably improved and was able to sit at the table with the family and eat. She remained febrile throughout this time, however. One day before admission to hospital she appeared worse to the family. She complained of generalized pain as well as pain in her left elbow. She was taken to the emergency room of a second local hospital where an analysis of urine was ordered but no urine was obtained. A blood test was interpreted as suggestive of infection. An x-ray study of the left elbow was said to show no abnormalities and the parents were instructed to continue with the administration of penicillin. The morning of admission she awoke again with fever; in the left axilla was noted a lump that was not erythematous and was nontender. She was taken to see her private physician, who noted the left axillary mass, the fever and a significant left shift of the complete blood count done in the emergency room the night before. He then referred the child to Childrens Hospital for admission.

Her past history was remarkable for Hemophilus influenzae B cellulitis at the age of 9 months. Growth and development had been normal and she lacked immunization boosters for diphtheria-pertussis-tetanus immunization and oral polio-vaccine. Review of systems revealed she had not been around any ill children. She had received no recent injuries and had ingested nothing unusual. She had been constipated for several days but had had a normal bowel movement early in the day of admission.

Physical examination revealed a well-developed girl, with a heart rate of 140 per minute, shallow respiration at a rate of 70 per minute, blood pressure of 120/80 mm of mercury and temperature of 39.3°C (102.7°F). Her skin appeared to be somewhat dry and mottled. There were no rashes, petechiae or purpura noted. Results of ear, nose and throat examination were essentially normal. The chest was clear to auscultation. The liver was palpated approximately 4 cm below the right costal margin and was smooth and nontender. A spleen tip was barely palpable. A 3-cm left axillary mass was nontender and nonerythematous and was not warm to touch. Neurologic examination showed an alert, awake and active child who was otherwise normal.

Approximately 30 minutes after admission to hospital, she experienced increasing tachypnea. Re-examination at that time revealed no other differences from results of the initial examination. She had a second normal bowel movement at that time.

An hour after admission, her skin appeared to be somewhat more mottled than previously, but she remained alert with appropriate behavior while an intravenous infusion was being started. Because of the difficulty in starting the intravenous infusion and concern about increased mottling with continued tachypnea, she was transferred to the intensive care unit for closer monitoring and placement of a cutdown. Immediately after transfer she vomited, suffered a generalized tonic-clonic seizure with stiffening of all extremities and arching of the neck, became cyanotic and had a cardiopulmonary arrest. She was promptly intubated and resuscitated. A cutdown was placed in the right saphenous vein. She was given 100 percent oxygen and was given bicarbonate, epinephrine, calcium and isoproterenol hydrochloride (Isuprel®). In spite of vigorous cardiac pulmonary resuscitation, the patient did not respond; she was pronounced dead after an hour and 20 minutes. Subsequent laboratory data on the day of admission revealed a leukocyte count of 41,000 per cu mm, hemoglobin of 11 grams per dl and Gram-negative rods were reported seen on the peripheral smear with Wright stain.

Dr. Connor: What I would like to do in a few minutes is to point out the pathogenesis of plague starting with the biting flea. I would like to also point out the milestones that we can identify as being important in the cycle of pathogenesis and in some way relate to that cycle the clinical events that might be recognizable and helpful in the development of a diagnostic suspicion that would allow case diagnosis.

Figure 1 is the kind of scheme I have used to acquaint myself with pathogenesis of plague. At the top of the figure is shown an event that is generally uncommon in pathogenesis of disease; that is, an injection of nonvirulent bacteria progressing to generalized fatal infection through mechanism and factors contributed by the infected host.[4] Most of the 1,000 to 12,000 bacteria that are injected during the regurgitant feeding of the vector flea are killed at the site by phagocytosing neutrophilic leukocytes. There is usually no inflammation at the bite site; sometimes a minute abscess develops but that is in-

frequent. However, despite phagocytosis by the host of most of the infected bacilli, an essential step in the survival and ultimate progression of the infection also occurs at the site or within inguinal lymph nodes; that is, engulfment by monocytes but survival of intracellular bacilli allowing replication in the host at a higher temperature. Therefore, during the incubation period of three to seven days, there is initial replication within the host's monocytes at a temperature that provides increasing virulence. The differential between flea temperature of 28°C and temperature of 37°C (82.4°F and 98.6°F) in the host provides for a change—not a mutation—in the bacterium from avirulent to virulent form. During that time, plague bacilli become highly encapsulated and acquire factors known as virulence factors V and W. The incubation period thus is the first and essential phase in pathogenesis of plague.

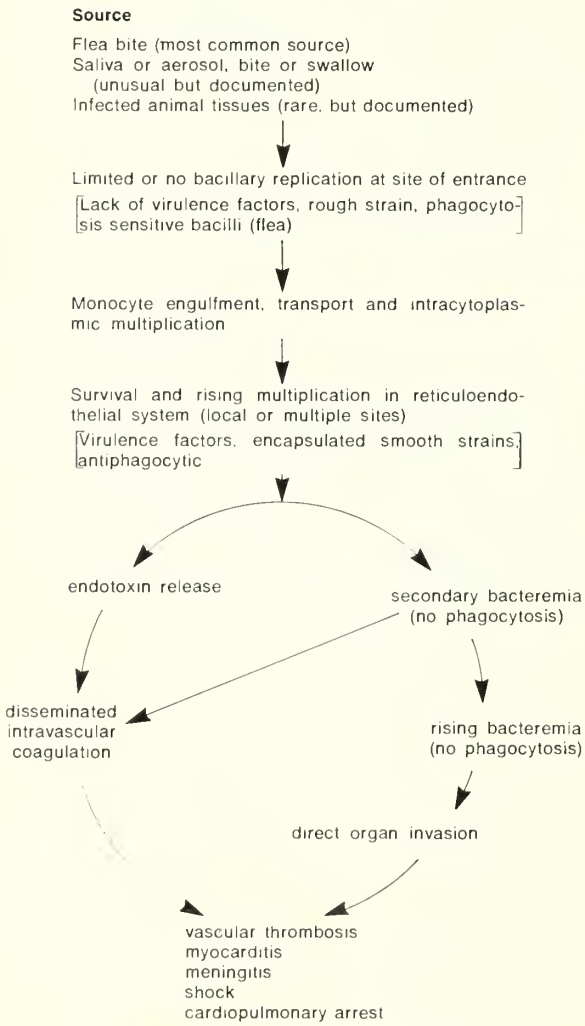

Figure 1.—Pathogenesis of plague.

TABLE 1.—*Differential Diagnosis of Bubonic Plague*

Lymphadenitis, acute
streptococcal
staphylococcal
granuloma inguinale
lymphopathia venereum
Pasteurella tularensis
cat-scratch disease
Pasteurella multocida
mycobacteriosis (atypical, fast grower)
Pharyngeal diphtheria
Acute parotitis
Peritonsillar abscess
Appendicitis
Hip-joint pyogenic arthritis
Mesenteric lymphadenitis

During the second phase, rapid bacterial replication occurs within one or more lymph nodes, provided for by the antiphagocytic nature of the virulence factors. Encapsulated plague bacteria, replicating at animal body temperature, are highly resistant to phagocytosis and killing. Therefore, the progression of the infection within the regional lymph node is relatively rapid and virulent, leading to development of local inflammatory signs and concomitant systemic complaints, usually at the same time.

In 95 percent of all cases of plague, patients present with one enlarged node, a regional lymph node draining the bite site.[3] Enlarged nodes may be found at different locations throughout the body, most commonly in lower extremities where they are more frequently femoral and inguinal nodes, less commonly in upper extremities where they are more frequently axillary and less frequently epitrochlear. Nodes appear less commonly in the neck and are least frequent in the anterior cervical region. The lesson is that almost any area of regional adenopathy may present, including deep glands such as the iliac or deep cervical, making the immediate diagnosis sometimes very complicated.

Due to the rapidly expanding node infection, pain at the site and in the area of involvement may be most severe; the pain may be so great at the site or within the quadrant of involvement that the lymph gland involved may be overlooked or thought not to be the cause of pain. I think such findings should increase the index of suspicion more than the similar ones that occur in a broad, recognized etiologic spectrum of lymphadenitis (Table 1). The infected lymph gland

that is involved may be the site of so much pain that the entire joint or quadrant may be immobilized from the day of onset. The pain of the lymph gland, upon examination, is usually exquisite particularly in the early phase, regardless of size. As the gland expands and finally suppurates, the pain may be less. This is easily confused with pyogenic arthritis, deep inguinal adenitis of streptococcal origin and similar syndromes in deep nodes. Frequently in bubonic plague no involvement of soft tissue is recognized; later involvement of soft tissue is usually characterized by inflammatory edema with or without erythema. These findings, exquisite pain and tenderness with immobilization of the quadrant or an extremity would point toward adenitis of plague infection as well as toward other kinds of frequent diagnoses we make in pediatric patients.

To return to continuing pathogenesis: A systemic reaction is also occurring at the time, depending upon production by replicating bacteria of typical Gram-negative bacterial endotoxin or an exotoxin peculiar to the plague bacillus, as yet poorly characterized. The progress of this stage is rapid due to the fact that phagocytosis does not work in either monocytic cells or neutrophilic cells. Therefore, rapid replication continues; bloodstream invasion occurs secondarily, and bacterial replication occurs there also. This stage is accompanied by a feeling of intense illness in the patient. Right from the first day of illness the patient may have high fever, a sense of prostration, a feeling of impending doom, lethargy, chilly feelings or overt chills, and may be septic out of proportion to what you may find on physical examination at that time.

If untreated, the last stage of this progressive syndrome goes on to be marked bacteremia. Some findings out of the Vietnam experience of the 1960s reported by Butler[5] point out rising bacteremia with maximum bloodstream infection with 10^2 to 10^6 bacteria per ml of blood. Shock and death are common consequences of that condition as contrasted to nonbacteremic bubonic plague, in which mortality is much lower.

At this stage, San Diego's patient had a marked bacteremia, and bacteria were noted in a peripheral smear of her blood (Figure 2). In such a smear polymorphonuclear cells are characteristically found in large numbers without any evidence of phagocytosis. The plague bacillus also induces an anti-opsonin factor in blood and progressively arranges for itself "free" replication within tissues, organs and blood. In lethal infections, the end comes as a direct result of massive bacterial invasion in blood and tissue; relative to that, plague endotoxin activity is probably of lesser relative importance.[6] Vascular thrombosis, myocarditis and meningitis all occur, as well as shock and cardiopulmonary arrest, as developed in the patient we are discussing. The rapidity of the lethal infection is brought out by this case. Physicians have precious little time to act; a period of only three to five days to mount an appropriate diagnostic and therapeutic response is not unusual.

Differential diagnosis of bubonic plague includes a number of childhood infections (Table 1). Some characteristics of these infections do match up with plague diagnosis, some obviously do not. I offer the list only to indicate that this is the kind of pediatric infectious disease spectrum we might think about and to stress that plague should be included in it, in San Diego, regardless of the fact that we have only seen one case and that in 1977. We need to develop an index of suspicion and appropriate screening for plague along with other conditions in the differential diagnosis of cellulitis and lymphadenitis.

Unlike most hard, tender, nonfluctuant lymph glands, the plague-infected gland should be needled to make an immediate diagnosis; the diagnosis can be established by providing the laboratory with appropriate specimens. Needle aspiration of the nonfluctuant node or excision should probably be done under antibiotic therapy to prevent bacteremia as a result of manipulation. It should be done immediately upon developing

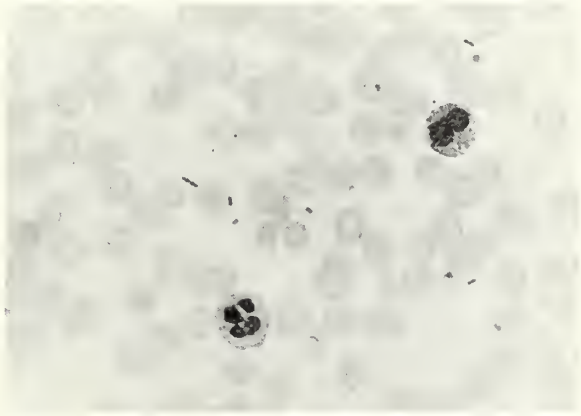

Figure 2.—Peripheral blood smear illustrating massive bacteremia.

TABLE 2.—*Epidemiological Circumstances Favoring Diagnosis of Plague*

Nonurban residence (particularly southwestern part of United States)
Domestic cats or dogs known to have wild animal contact
Sick animal contact, recently
Recent camping or sleeping on the ground
Known flea bites
Known plague area, visit or residence
Plague in the family or community, recently

a clinical index of suspicion. The node should be entered with a needle and a saline wash of the gland should be sent to the diagnostic laboratory for stain and culture. If removed surgically, the node should be used also to make imprints on a slide to search for plague bacteria. This situation is unusual to pediatricians and surgeons alike in that we usually do not aspirate small, tender, hard nodes but wait for fluctuation. However, it is not appropriate to wait for staging or fluctuation in plague. When node fluctuation is present, pus can be taken for an immediate diagnosis. If the lymph gland involved is deep, a physician may not be suspicious of plague; clinical suspicion is usually based upon characteristic physical findings. In some cases published in the radiological literature, deep lymph nodes involved by bubonic plague were visualized on radioscan.[7,8]

When the clinical index of suspicion has been reached, epidemiological factors may obligate prompt consideration of plague in the differential (Table 2). Such factors are important in developing an appropriate differential diagnosis. Considering experience in California and the southwestern United States, there should have been some recent contact by the family group of the patient with the outdoors or with animals that are in contact with the outdoors or with wild animals, or travel to an area of endemic animal plague where insect vector and the rodent host are known to come together in order for plague to be considered strongly in the differential diagnosis. However, recent reports also tell about sick domestic cats transmitting plague to owners and children. Doctor Ginsberg will talk more about such epidemiological factors in the latter part of this conference.

The mortality of bubonic plague, appropriately treated with antibotics, is low, less than 5 percent. The diagnosis can be established in time to arrive at that satisfactory result. The syndrome and the bacterial infection respond dramatically to antibiotics. Pharyngeal plague, a subset of bubonic plague that occurs in adults, is a mild condition also called pestis minor and is the only non-life-threatening variety of this disease recognized. Primary septicemic plague comes from already virulent sources of plague infection, such as an infected animal host—from the lick of a dog or from a cat with adenitis in which the infecting bacteria already have achieved encapsulation and virulence. No symptomatic node infection develops. The patient is very soon drastically ill with septicemia and bacteremia and dies in three or four days. Pneumonic plague is a similar kind of syndrome in which human-to-human transmission brings about devastating, rapidly fatal disease. A California veterinarian died recently of this form of disease acquired from an infected dog—not a person—transmitted during postmortem examination of the animal carcass.

Streptomycin probably is the drug of choice even yet—with 20 to 50 mg per kg of body weight per day by intramuscular injection yielding a low mortality in bubonic plague. With streptomycin, there is some controversy about the problem of Jarisch-Herxheimer reaction, but this probably is not clinically important. It may be important to add a systemic antibiotic by the intravenous route since meningitis has been reported to have developed in patients receiving streptomycin intramuscularly. Although tetracycline is a very good drug, it is difficult to give intravenously; moreover, among other disadvantages, it is painful, stains teeth, and is stored in bone. Chloramphenicol by the intravenous route is probably the drug of second choice as it rapidly controls bacteremia and prevents the late occurrence of meningitis. It is important to use two drugs in bubonic plague and these are the drugs of choice.

ROGER A. WILLIAMS, MD:* Doctor Connor has discussed the pathogenesis of plague, and I think you will see that this particular case demonstrates well the pathogenic mechanisms that result in fatal bubonic plague.

The presence of large numbers of plague bacilli seen in the peripheral blood smear (Figure 2) illustrates the massive, uninhibited multiplication of these bacteria after they have been activated and have become resistant to phagocytosis by the phagocytic cells of the host.

In the axillary bubo, other pathogenic features of the plague bacilli can be seen in the extensive

*Chief, Pediatric Pathology, Childrens Hospital and Health Center.

hemorrhagic tissue necrosis caused by large numbers of bacilli (Figure 3). On high-power examination of the lymph node we can see tremendous numbers of bacilli forming sheets of organisms which replace the previously existing lymph node architecture, notably without much of a suppurative reaction (Figure 4).

Similar hemorrhagic and necrotizing changes were noted in the heart, involving myocardium, endocardium and epicardium, again with large numbers of organisms present in the necrotic foci. As before, no significant suppuration was noted. These foci of hemorrhage can be seen grossly as petechial hemorrhages or small ecchymoses.

In the lungs, similar areas of hemorrhage and necrosis with multiplication of organisms were noted, most prominently in a perivascular distribution related to large and medium-sized pulmonary arteries and veins. In addition, the lungs demonstrated another mechanism of pathogenesis of plague, that of disseminated intravascular coagulation. In many of the small pulmonary blood vessels are thrombi in which moderate to large numbers of plague bacilli are enmeshed (Figure 5).

Microthrombi related to disseminated intravascular coagulation were widespread in a variety of other organs including the liver, spleen and kidneys. On gross examination, the spleen and liver were found to be enlarged; microscopic examination of these organs showed clusters of organisms in the sinusoids. The kidneys were severely affected, with a number of petechial hemorrhages over the surface and widespread involvement of glomerular capillaries and renal arterioles with microthrombi incorporating variable numbers of bacteria (Figure 6).

In summary, the pathogenic mechanisms of plague are well demonstrated in the pathologic anatomy of this patient, manifested by uninhibited multiplication of large numbers of bacteria, hemorrhagic tissue necrosis and disseminated intravascular coagulation.

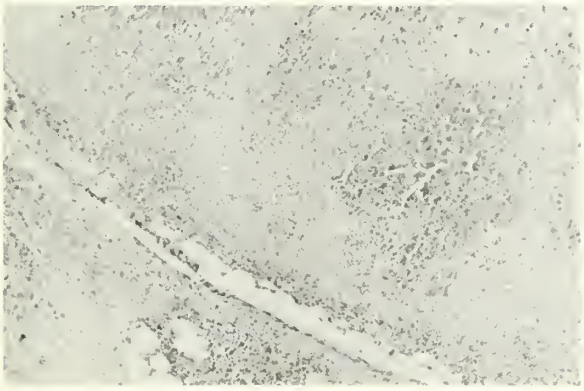

Figure 3.—Hemorrhagic tissue necrosis with massive tissue invasion by plague bacilli.

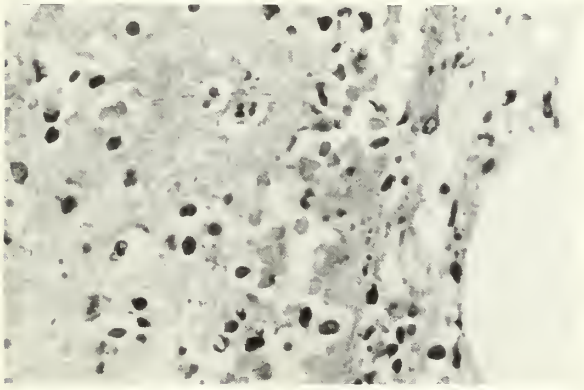

Figure 4.—Numbers of bacilli forming sheets of organisms which replace the previously existing lymph node architecture, without much suppurative reaction.

MURIEL A. THOMPSON, DRPH:† Regarding laboratory aspects of Yersinia pestis identification, the specimens that come to the laboratory for diagnosis may consist of aspirates, blood, sputum, throat swabs or autopsy material; or, as in this particular case, the isolation may come from spinal fluid. I think that the hospital microbiology laboratory is to be commended for the identification and for rapid assistance in the diagnosis of this case. I stress the need to pass along the case history with specimens submitted to the laboratory; in this case, the accompanying history prompted personnel of the hospital

†Chief, Public Health Laboratory.

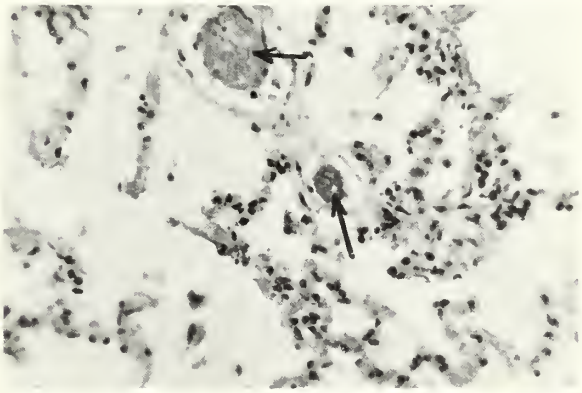

Figure 5.—Thrombi enmeshed with plague bacilli in small pulmonary vessels.

laboratory to consider plague in the differential diagnosis.

The bacteriology of plague began in 1894 in Hong Kong, with the discovery of the organism by Alexandre Yersin, who identified and classified the bacillus. The organism is a Gram-negative, aerobic, facultative-anaerobic, non-spore-forming coccobacillus, relatively large, with slightly pointed ends, a characteristic that helps to differentiate it from other bipolar-staining organisms. Wayson stain,[9] a combination of carbol-fuchsin and methylene blue, is better than Wright stain to show up the bipolar characteristic. The organism grows easily and readily on most media. The colonies at 24 hours are tiny, but at 48 hours they measure 1 to 2 mm and are quite easily recognizable. They grow well in most hospital laboratories upon a 5 percent blood agar base. The optimum temperature of growth is 28°C. However, for a number of the diagnostic tests, the organisms must be cultivated at about 30°C. Our laboratory procedures usually call for 35°C so that fraction I (the capsular or envelope, heat-labile, protein antigen of Y. pestis),[10] which is important in diagnostic tests, will be found. The organism is of the Enterobacteriaceae group and resembles Pasteurella. However, the pasteurellae are oxidase-positive and since the plague bacterium is oxidase-negative, it has been recently reclassified as a member of the Yersinia genus. Also reclassified are Y. pseudotuberculosis and Y. enterocolitica, all of which are oxidase-negative. The organisms are routinely nitrate reducers and attack carbohydrates.

Approximately 30 to 40 biochemicals may be used in the laboratory in order to come to a final

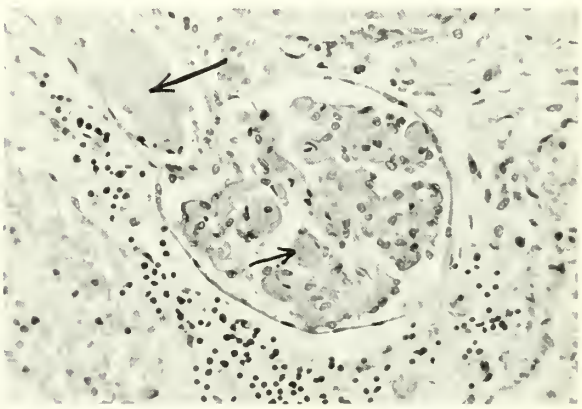

Figure 6.—Widespread involvement of glomerular capillaries and renal arterioles with microthrombi incorporating numbers of bacteria.

TABLE 3.—*Biochemical Reactions of Yersinia pestis After 48 Hours of Incubation at 37°C*

Biochemical	*Reaction*
Triple sugar iron agar	No change to slight A/A
Kliglers iron agar	No change to slight A/A
Nitrate reduction	+
Methyl red	+
Voges-Proskauer	−
Indol	−
Esculin hydrolysis	+
Litmus milk	No change
Gelatin hydrolysis	−
Salicin	−

A = acid

NOTE: Reactions noted were shown on 35-mm color film supplied by Thomas Quan, PhD, Plague Branch, Center for Disease Control, Fort Collins, Colorado. (This table reprinted by permission from Dr. Quan.)

bacteriologic identification (Tables 3, 4 and 5). Bacteriologists should note that, in the chart on page 224 of the *Manual of Clinical Microbiology,* second edition,[11] the salicin reaction is indicated to be positive for Y. pestis; our culture was negative, a result that coincided with reference information from Dr. Thomas Quan of the Center for Disease Control (this may be a variable reaction, according to *Bergey's Manual,* eighth edition[12]). A summary of the biochemical reactions most helpful in differentiating the three species of the genus Yersinia is shown in Table 5.

In a 24-hour broth culture at room temperature, the organisms tend to adhere to the side of the tube and thus appear to be motile, although the organism is nonmotile. If such a culture is gently shaken, the growth simply settles to the bottom of the tube.

The phage lysis test is helpful in the specific identification of Y. pestis versus the other Yersinia. In the phage test, all strains of Y. pestis and also Y. pseudotuberculosis grown at 35°C will be lysed by the phage. Y. pseudotuberculosis, however, is not lysed at 20°C, whereas Y. pestis is. There is a simple procedure: Single streaks of the unidentified organism and of each control organism (for example, Y. pestis and Y. pseudotuberculosis) are made on blood agar plates. The streaks are overlaid with a filter-paper strip that has been impregnated with the specific bacteriophage (Figure 7). The organisms are then allowed to grow at both room temperature and at 37°C.

A second test that is especially useful in early diagnosis is the fluorescent antibody (FA) staining technique. In the direct FA procedure, the organisms are stained with antiserum to Y. pestis

TABLE 4.—*Biochemical Reactions of Yersinia pestis After 24 Hours of Incubation at 37°C*

Biochemical	*Reaction*	*Biochemical*	*Reaction*
Triple sugar iron agar	No change to slight A/A	Mannitol	+
Kligers iron agar	No change to slight A/A	Mannose	+
Oxidase	−	Arabinose	−(V)
Catalase	+	Fructose	+
Phenylalanine deamination	−	Galactose	+
Glucose	A, no gas	Melibiose	weak +
Glucose fermentative (OF)	A	Raffinose	−
Glucose oxidative (OF)	A	Rhamnose	−
Urea	−	L-sorbose	−
Citrate	−	Trehalose	+ (V, usually +)
Arginine dihydrolase	−	Xylose	+
Lysine decarboxylase	−	Adonitol	−
Ornithine decarboxylase	−	Dulcitol	−
Lactose	−	Inositol	−
Sucrose	−	Sorbitol	+

A = acid
V = variable

NOTE: Reactions noted were shown on 35-mm color film supplied by Thomas Quan, PhD, Plague Branch, CDC, Fort Collins, Colorado. (This table reprinted by permission from Dr. Quan.)

that has been conjugated with fluorescein isothiocyanate. Only Y. pestis will fluoresce if specific conjugate is used. Y. pseudotuberculosis and Y. enterocolitica used as controls should not stain. In the case under discussion, we ran into some problems. We had received antisera designated as specific for Y. pestis. We did the FA stain procedure in our laboratory on the culture forwarded to us. We observed varying levels of fluorescence with the various Yersinia species available; that is, unidentified organisms showed 4+ fluorescence, whereas the Y. enterocolitica and Y. pseudotuberculosis used as controls showed 2+ readings. Then we learned that the one reference laboratory that had furnished conjugate had used mixed Yersinia antigen in developing the diagnostic antisera. They did not absorb it, and as a result all organisms of the genus stained with the tagged antibody. The other reference laboratory, from which we were able to get conjugate within a couple of days, had a specific reagent that stained only Y. pestis. Once so standardized, the FA test is an excellent diagnostic procedure. It is currently available in our laboratory if you should have a problem identifying or excluding Y. pestis in clinical isolates.

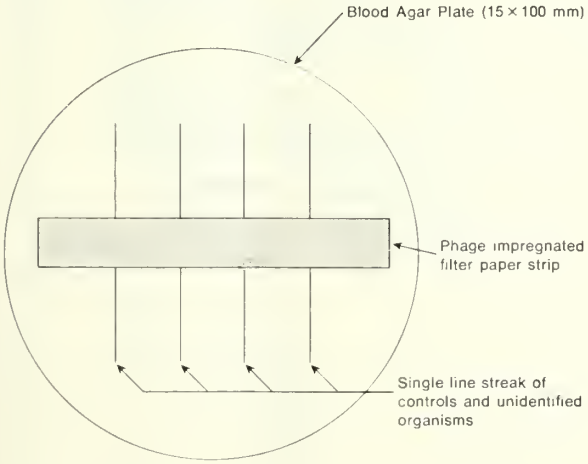

Figure 7.—Procedure for setting up phage test for Yersinia pestis. Prepare 2 identical plates. Incubate one at 20°C and one at 35-37°C.

TABLE 5.—*Key Differential Biochemical Reactions of the Genus Yersinia*

*Biochemical Reactions**	*Y. pestis*	*Y. enterocolitica*	*Y. pseudotuberculosis*
Oxidase	−	−	−
Catalase	+	+	+
Motility at 22°C	−	+	+
Motility at 37°C	−	−	−
Urease (Christensen)	−	+	+
Indol	−	+ or −	−
Methyl red	+	+	+
Voges-Proskauer	−	−	−
Citrate (Simmons)	−	−	−
Lactose	−	Slow A	−
Sucrose	−(V)	A	−
Melibiose	Weak A	−	A
Sorbitol	A (V)	A	−
Salacin (48 hours)	−(V)	−(A)	A
Esculin (48 hours)	+	−	+
Adonitol	−	−	A (−)
Ornithine decarboxylase	−	+	−
Triple sugar iron agar	ALK/A	A/A	ALK/A

A = acid
ALK = alkaline
V = variable
*Cultures incubated at 35°C for 24 hours unless otherwise indicated.

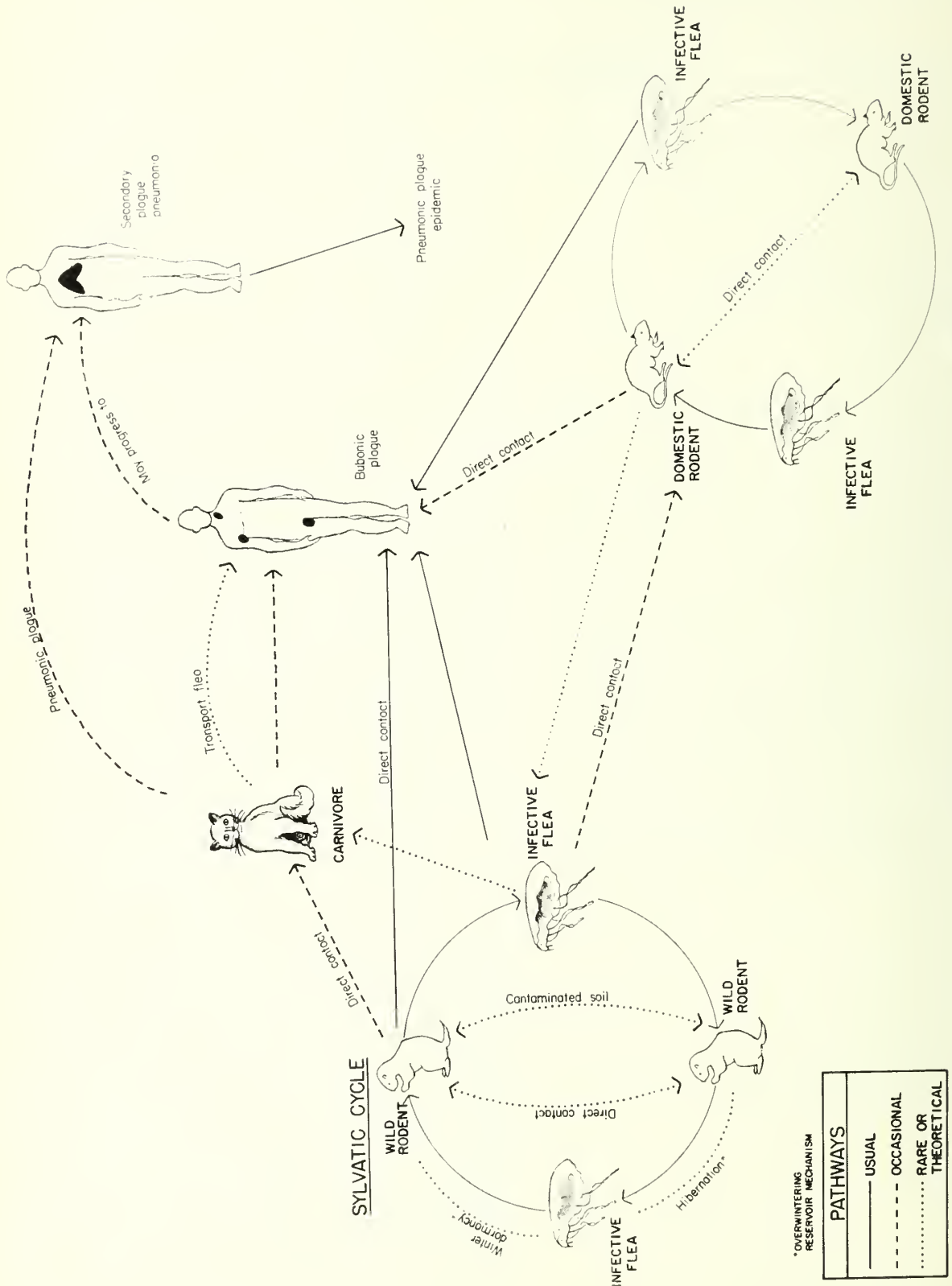

Figure 8.—Cycles of plague (adapted and reprinted with permission from Kartman L. Goldenberg MI, Hubbert WT: Recent observations in the epidemiology of plague in the United States. Am J Public Health 56:1554-1569, Sep 1966).

The passive hemagglutination procedure is also available and is an excellent test to assist in diagnosing plague. The organism with fraction I^2 present will cause the development of antibodies that will be demonstrated by this procedure; current infection is indicated if a fourfold rise is shown. Since a very low percentage of the population has the antibody, even a titer of 1:16 is presumptive of a current or recent infection with Y. pestis.

MICHELE GINSBURG, MD:* As has already been indicated, plague is an aggressive disease. It has been called black death and the great pestilence. Since the 13th century BC, it has been a decimator of human populations. It remains so today but is a relatively infrequent cause of death in developed countries.

Plague in the United States must be considered in three cycles: in the sylvatic or wild rodent population, in the domestic or urban rodent population and in the human population (Figure 8). Y. pestis, the plague bacillus, can survive in the flea-rodent cycle without involvement of humans. However, when a person is bitten by an infected flea, bubonic plague develops initially. If the person does not receive prompt, specific attention, sepsis occurs and secondary plague infection of the lung may follow. Once lung infection develops, plague may be transmitted as an airborne disease and has the potential of infecting many people without an insect vector.

Plague first entered the United States in 1894 by means of ships from Asia that docked at the port cities of San Francisco, New Orleans and New York. Infection became established in the domestic rodent population. The last outbreak of pneumonic plague in this country occurred in Los Angeles in 1924.[13] During that outbreak, of 32 patients with pneumonic plague, 30 died. Seven bubonic plague cases were identified as well.

As plague in the domestic rat population was controlled, it became established in the wild rodent population, where it has remained endemic. Since 1924, all known instances of plague in humans in the United States have resulted from contact with the wild animal population. In California alone, plague has been identified in 136 persons, of whom 71 died, a 52 percent mortality rate.[14]

Domestic (urban) plague is not a thing of the past. As recently as 1968, domestic rodents in Denver were identified as being infected with plague. Domestic rats acquired their infection through mingling with the rural rodent population

*Epidemiologist, Bureau of Disease Control, Department of Public Health, County of San Diego, and Clinical Instructor, Departments of Medicine and Community Medicine.

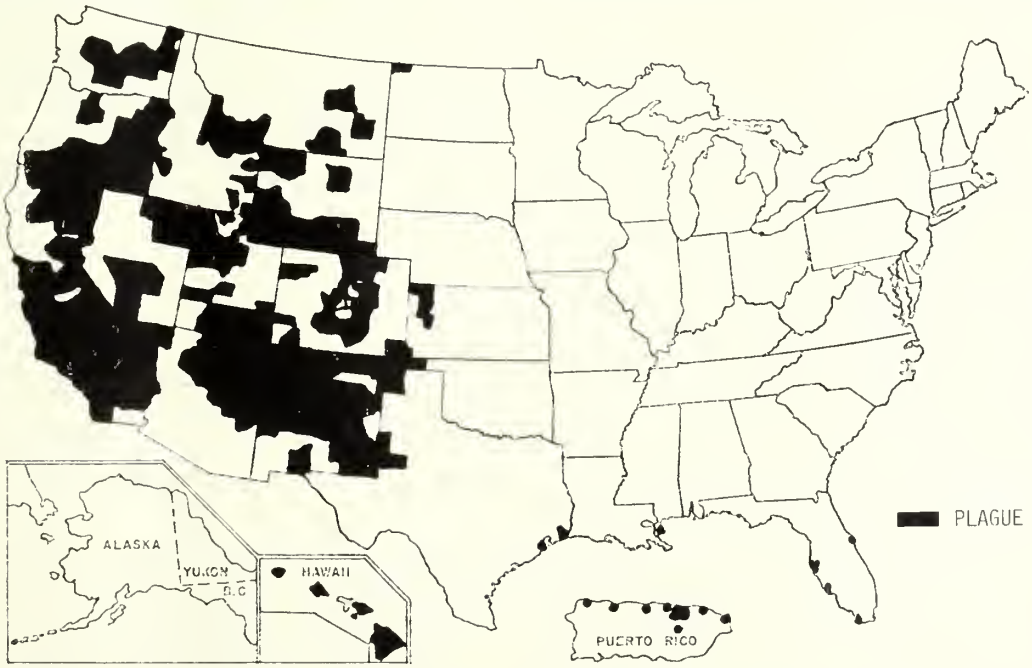

Figure 9.—Endemic areas of plague infection in animals in the United States from 1908 to 1969. (Adapted with permission from Center for Disease Control, Plague Surveillance Report No. 1, 1970.)

of that mountain city. Only through an active surveillance and rodent-control program was an outbreak of plague in humans prevented.

In order for plague to persist in wild animals, it must infect a relatively resistant animal population. Since fleas can survive the winter in animal burrows, young rodents can become infected and perpetuate the cycle of wild rodent infestation each spring. In the western United States, plague infection has been found in ground squirrels, prairie dogs, chipmunks, rabbits, mice and rats, as well as in larger carnivores, such as bobcats and coyotes.[15]

Humans become involved with plague when they enter into the sylvatic cycle. For example, a person may become infected by handling a dead squirrel or by skinning a rabbit or a bobcat. On the other hand, an infected flea may leave a dead or dying rodent and attach itself to a human for a blood meal (a contact resulting in a case of bubonic plague). When people take pets into the wild or woodland area, the pets may catch infected animals and transport fleas back to their masters. Dogs are relatively resistant to plague and after exposure may show seroconversion without evidence of clinical illness. Cats, on the other hand, are quite susceptible to plague, and two of the 18 cases of plague in humans reported in 1977 by Allan M. Barnes, PhD, Chief, Plague Branch, Bureau of Laboratories, Vector-borne Diseases Division, Center for Disease Control, Fort Collins, Colorado (personal communication, November 1977) resulted from contact with infected cats.[16,17]

TABLE 6.—*Human Plague Cases in the United States, Incidence and Mortality, 1975-1977*

Year	Males		Females		Total Cases
	Cases	Deaths	Cases	Deaths	
1975	5	1	15	3	20
1976	8	2	8	1	16
1977	12	1	6	1	18
Total ..	25	4*	29	5*	54

*Mortality: males, 16 percent; females, 17 percent.

The endemic areas of plague infection in the United States are illustrated in Figure 9. Fifteen western states on both sides of the Rocky Mountains have been extensively involved with plague in the wild rodent population. Because plague persists in these wild rodent populations, it is possible for plague to be reintroduced into the cities as a result of animal commingling. In San Diego, plague was identified in wild rodents dur-

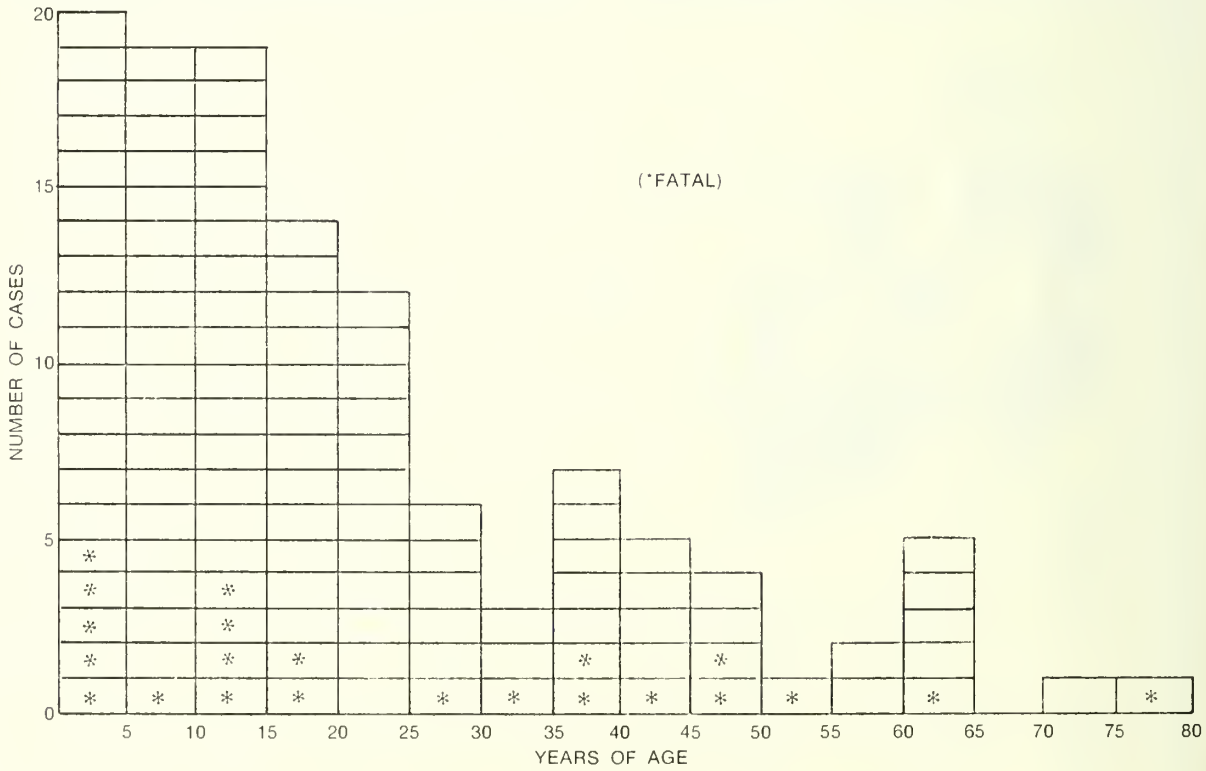

Figure 10.—Plague cases in United State from 1950 to1977.

ing the 1940s; but, as Dr. Connor indicated, no plague infection in persons has originated through animal contact in San Diego County.

Plague is actually an international disease found in countries on most continents, including Canada, Brazil, India and Russia. For example, an annual incidence as high as 6,500 cases of plague was reported in Vietnam during the 1960s. Plague may occur throughout the year; but, in this country, most infections have occurred in the period from June through September.

Figure 10 represents the 119 plague cases reported in this country from 1950 through 1977. All age groups are represented, but three fourths of the cases have involved patients under the age of 25. No age group is spared from mortality from this disease.

The sex distribution of plague cases in the United States during a recent three-year period is illustrated in Table 6. It was formerly believed that males were much more likely to be affected by the plague than females, but now that females participate more in wilderness activities, their incidence rates have approached male rates. Mortality rates have been about the same for both sexes. Of the 54 patients with plague reported during the three-year period shown in Table 6, 15 developed pneumonic involvement and with it the risk of person-to-person transmission.

It is important for clinicians to consider plague in the differential diagnosis, especially in young persons with enlarged lymph nodes and fever after camping or hunting in the western states. Once the diagnosis is considered, the physician is obligated to treat the patient with specific drug therapy, collect the appropriate specimens, such as by aspiration of a bubo, and then attempt to rule out the diagnosis using the specific fluorescent antibody test as well as culture of the specimen. The Health Department must be notified; it can assist in making the specific diagnosis of plague from the clinical material and can help in defining exposure to other contacts.

In the hospital, the patient must be placed in strict isolation until the extent of infection is established. Since Y. pestis is transmitted by droplets, airborne spread can occur between persons who have had prolonged close contact. It is noteworthy that no secondary cases have occurred in the United States since 1924, even though many patients in recent years have developed pneumonic complications. We can probably attribute this absence of secondary cases to the fact that extensive prophylaxis has been offered to contacts.

Once the diagnosis of bubonic plague is established, there is usually little risk to contacts since treatment is effective against the bacterial infection. However, strict isolation should be observed, and contacts should be placed under surveillance, which should include determination of temperature twice a day. In addition, specific therapy (tetracycline or streptomycin or both) should be initiated at the first sign of fever or other illness. If a diagnosis of pneumonic plague is established either by clinical presentation or by autopsy examination (as in the patient discussed today), chemoprophylaxis in contacts should be instituted immediately. In our case, all 48 persons who had contacts with the child during the last 24 hours of her life were located, and all were treated with tetracycline or sulfadiazine. Therapy should continue for ten days and temperature of contacts should be taken twice daily, with immediate reporting of elevation of temperature. In a child contact, tetracycline should be avoided; sulfadiazine is recommended, 75 mg per kg of body weight per day in four divided doses for a ten-day period. For adults, 250 mg of tetracycline every six hours may be administered for ten days.

Once a diagnosis is established, the source of infection must be identified. For this case, two of the three campgrounds visited by the family showed flea pools positive for Y. pestis. Both these areas were treated by exterminators to reduce the infected animal population and, it is hoped, to prevent future infection of persons.

Appropriate precautions can be taken to minimize the risk of exposure to plague. Vaccination is not recommended for campers, but patients should be advised not to handle sick or dead animals in the woods or at home. Sleeping bags should not be placed directly on the ground, and tents or sleeping bags should not be placed near entrances to animal burrows. Insect repellents can be used in the woodland areas and pets should be kept leashed and should be deflead after returning home.

A physician must be alert to the possibility of plague infection. Patients should be asked about exposure to wild animals and about camping or hunting experience in a plague endemic area

within the preceding week. The only way to defend against plague and to reduce mortality is by suspecting the problem, making an early diagnosis, and initiating treatment as soon as the diagnosis is suspected.

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Thick Nasal Antral Walls in Chinese

I HAVE A GOOD FRIEND who practices in Taiwan. He tells me that when he is doing a sinus irrigation on his countrymen, he always has a little mallet on the tray. This is to hammer the trochar through the medial wall of the sinus in very young, delicate Chinese ladies. Apparently the antral wall in the Chinese is often much thicker than in Caucasians.

—PAUL J. DONALD MD, *Davis, California*

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Refer to: Uric acid, diuretics and the kidney—Medical Staff Conference, University of California, San Francisco. West J Med 129:407-411, Nov 1978

Uric Acid, Diuretics and the Kidney

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and Robert C. Siegel, Associate Professor of Medicine and Orthopaedic Surgery, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *This Medical Grand Rounds will consider uric acid, diuretic drugs and the kidney, and Dr. David G. Warnock will discuss this topic.*

DR. WARNOCK:† Uric acid is the end product of purine metabolism in humans, and it is excreted by the kidneys.[1,2] This morning I should like to review three aspects of the relationships between uric acid and the kidney: (1) the renal transport mechanisms for uric acid, (2) the effects of hyperuricemia upon the kidney and (3) the clinical setting in which asymptomatic hyperuricemia develops, such as during the treatment of hypertension with thiazide diuretic drugs.

It is generally agreed that at least four components are involved in the renal handling of uric acid.[1,3] These components are summarized in Table 1. The first component is the filtered load of uric acid which is delivered to the nephron. The second component is an avid reabsorptive process which reclaims nearly all of the filtered uric acid load. Another component is a secretory process that provides most of the uric acid which is ultimately excreted in the urine. Last, there is another reabsorptive site which is farther downstream. This last component modulates the final excretion rate of uric acid and may be an important site of action of agents that increase the rate of uric acid excretion in the urine.

Let us consider how much uric acid is presented to the kidney and how much is excreted.[4] The filtered load of uric acid amounts to about 8.5 grams per day if we assume that uric acid is freely filtered. We shall ignore the amount of urate that is bound to plasma proteins (approximately 20 percent). The daily excretion rate for uric acid is normally less than 800 mg. Therefore, there must be an avid tubular mechanism which reabsorbs at least 90 percent of the filtered load of uric acid (Table 2). If normal subjects are loaded with purines to increase the filtered load of uric acid, a tubular reabsorptive capacity of at least 15 mg per minute can be shown.[4] Compare this reabsorptive rate, 15 mg per minute, with the typical filtered load of 6 mg per minute and you can appreciate the large capacity of the kidney for reabsorbing uric acid. This sort of bookkeeping leads us to the realization that there may be a secretory mechanism for uric acid.

The secretory process for organic acids has recently been localized in the middle third of the proximal tubule.[5] The middle third, or the S2

*Lloyd H. Smith, Jr, MD, Professor and Chairman, Department of Medicine.

†David G. Warnock, MD, Assistant Professor, Department of Medicine, Division of Nephrology.

TABLE 1.—*Renal Transport Mechanisms for Uric Acid*

Filtration
Reabsorption
Secretion
Postsecretory reabsorption

TABLE 2.—*Filtration and Excretion of Uric Acid*

Filtered Load	
(6 mg /dl) × (100 ml/min)	= 6 mg/min
	= 8,500 mg/24 hrs
Excreted	< 800 mg/24 hrs
Tubular Reabsorption	= 7,700 mg/24 hrs
Capacity	= 15 mg/min

segment, is morphologically distinct from the adjacent S1 and S3 segments of the proximal tubule. It is this middle third that has the secretory capacity for organic acids, such as para-aminohippurate (PAH). Its secretory rate is nearly four times that of the adjacent S1 and S3 segments. The secretory site has been described in both the superficial and juxtamedullary proximal tubule. The active step for organic acid secretion is located at the basolateral membrane of the tubule cells.[6,7] The organic acids are actively transported into the cells and accumulate in the interior. They then diffuse into the urinary fluid in the tubule lumen. It is important to realize that many organic acids, such as uric acid, PAH, lactic acid and ketoacids, and drugs, such as diuretics and penicillin, share the same organic acid secretory pathway. These agents can, therefore, compete for access to the active transport site on the blood side of the tubule. The result can be the hyperuricemia that may be seen in lactic acidosis and ketoacidosis and the paradoxical fall in urate excretion that may be seen with low doses of uricosuric agents, such as phenylbutazone, probenecid, salicylates and thiazide diuretic drugs. We shall consider the postsecretory reabsorptive site when we discuss the effects of diuretic drugs on uric acid excretion.

Let us turn to the effects of hyperuricemia upon the kidney. Does chronic asymptomatic hyperuricemia adversely affect renal function? The answer to this question is controversial. Emmerson and Graham Row,[8] in an editorial review replete with anecdotal experience, argue that chronic hyperuricemia causes a primary nephropathy by physical deposition in the renal interstitium and in the lumen of tubules. Superimposed infection, obstruction, calculi and hypertension secondarily contribute to further decreases in renal function. There has even been a specific glomerular lesion described in patients with hyperuricemia.[9] However, when this lesion was closely examined it could not be distinguished from hypertensive glomerulosclerosis.[10] As it turns out, patients with gout whose renal function is compromised are older patients who have hypertension and vascular disease. Furthermore, Rosenfeld[11] has shown in patients followed for three to four years that bringing uric acid concentrations to normal levels in patients with hyperuricemia has no beneficial effect on renal function. Berger and Yü[4] followed 524 patients with gout at intervals of up to 12 years, and in only a few instances were they willing to ascribe diminished renal function to gout. Hyperuricemia alone had no deleterious effects on renal function. Decreased renal function could be ascribed to aging, renal vascular disease, calculi with pyelonephritis, or other nephropathies, including hypertensive glomerulosclerosis. On the basis of their study, it does not seem necessary to treat asymptomatic hyperuricemia to prevent gouty nephropathy.

Let us change our focus from the amount of uric acid in the serum to consider the quantity which is excreted in the urine. There is a form of acute renal failure that can occur in patients with pronounced hyperuricemia and hyperuricosuria. Tubular obstruction by deposits of uric acid is important in the pathogenesis of this form of acute renal failure. This process is typically seen in patients with acute leukemia who are brought into remissions so that there is a huge outpouring of purines from the dying cells.[12,13] Massive urate excretion has also been reported to occur spontaneously in patients with lymphoma. To date, only 50 actual cases have been reported. However, it is important to recognize this form of acute renal failure because it responds dramatically to dialysis. This disorder can be recognized by its abrupt onset in the clinical setting in a patient who has predisposing disease and severely elevated levels of serum and urine urates. It is marked by oliguria and readily responds to dialysis. Forced diuresis and urine alkalinization have not been very successful, so these patients should be dialyzed early. Kelton and co-workers[13] compared five patients with acute uric acid nephropathy with 27 patients with other forms of acute renal failure. The five patients had acute leukemia and an average level of serum urate of 21 mg per dl. These authors made an issue of the urinary uric acid/creatinine ratio,

but this was only a reflection of the pronounced hyperuricemia and uric acid excretion in their patients.[13] There is another clinical setting in which tubular obstruction due to uric acid deposition has been invoked as a contributing factor to acute renal failure. In patients with exertional rhabdomyolysis acute renal failure may develop.[14] However, the hyperuricemia in these patients is modest compared to that in patients with leukemia, so that acute uric acid nephropathy is probably not a very important factor in this form of acute renal failure.

I mentioned the relation between hyperuricemia and hyperuricosuria, seen in its extreme form in patients with acute leukemia. We shall now consider nephrolithiasis. This problem seems to be more clearly related to the level of uric acid in the urine than in the serum. In patients with gout and hyperuricemia, nephrolithiasis can develop, but in most of these patients stones of calcium oxalate form.[15] Furthermore, most patients with established renal disease are hyperuricemic, but only rarely do renal stones develop in these patients. In patients with chronic renal disease, it can be shown that uric acid excretion falls as glomerular filtration rate falls.[8] Therefore, hyperuricosuria is not an important problem in patients with chronic renal insufficiency even though they do become hyperuricemic. When the clearance rate of urate is examined as a function of the glomerular filtration rate (GFR), it is interesting to note that the creatinine clearance rate falls more rapidly than that of urate.[4] As a result, uric acid excretion is relatively enhanced when the GFR is low and the level of serum uric acid is high. The relative enhancement of uric acid clearance rate in renal insufficiency can be explained by the relationship between the level of uric acid in serum and the rate of uric acid secretion. Berger and Yü[4] varied the levels of serum urate over a wide range in normal subjects, in patients receiving allopurinol (who therefore had low levels of serum urate) and in patients with hyperuricemia. They also studied a group of normal subjects who were fed large amounts of RNA to raise the levels of their serum uric acid. In these studies, Berger and Yü[4] estimated the secretory component of uric acid excretion by giving the patients pyrazinamide, an agent that is known to inhibit secretion of uric acid. Their results show that the secretory component assumes increasing importance as the level of serum uric acid increases. This finding explains the relative increase in uric acid clearance rates in patients with hyperuricemia and chronic renal failure. Therefore, we can expect that in some patients with renal failure and hyperuricemia acute gouty arthritis may develop, but nephrolithiasis due to hyperuricosuria will develop only rarely.

The last topic I should like to review is the problem of asymptomatic hyperuricemia that is discovered during a routine screening chemistry examination and the hyperuricemia that develops in patients who receive prolonged treatment with diuretic drugs. Hyperuricemia is a well-known effect of the thiazide diuretics, but it is also observed with more powerful "loop-diuretics," such as furosemide or ethacrynic acid.[16,17] The hyperuricemia seen with diuretic drugs is usually asymptomatic. Does asymptomatic hyperuricemia need to be treated? With regard to chronic gouty nephropathy, the answer is probably no. Lowering the level of serum uric acid will not halt or improve renal insufficiency, as discussed above.[11] With regards to acute gouty arthritis, the answer is also probably no. The Framingham study showed that in only 20 percent of patients with hyperuricemia acute gouty arthritis developed.[18] These episodes were brief and easily treated with nonsteroidal antiinflammatory agents. More importantly, only a fourth of these patients had more than one attack during the 12 years of that study. With regard to nephrolithiasis, the answer is probably no. The important determinant is the amount of uric acid in the urine not in the serum.[15] It is true that secretion of uric acid is enhanced when the level of serum uric acid is high, but this curve was relatively flat in the range of 6 to 9 mg per dl. If there is a tendency in a patient for stones to form, then the amount of uric acid in the urine should be determined.

Coe has reported that 25 percent of patients in whom calcium oxalate stones form excrete more than 800 mg (men) or 750 mg (women) of uric acid per day. He believes that there is a distinct clinical population in whom hyperuricosuric calcium oxalate stones form.[15] The mechanism linking hyperuricosuria to calcium oxalate stone formation is not known, but the incidence of new stone formation in this group does seem to be reduced by allopurinol.[15]

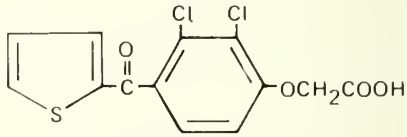
Asyptomatic hyperuricemia can best be managed conservatively. Liang and Fries[19] concluded

that the costs and risks of prolonged drug administration and other practical considerations, such as patient cooperation, mitigate against long-term therapy in asymptomatic patients. In fact, they calculated that the cost of taking allopurinol throughout a lifetime would be approximately $20,000.

How do thiazide diuretic drugs cause hyperuricemia? This question is important insofar as it can tell us something about the function of different parts of the kidney. In addition, a new therapeutic approach will soon be available for patients in whom hyperuricemia develops and who need long-term diuretic drug therapy. Ten years ago it was thought that thiazide drugs raised the levels of serum uric acid by causing volume contraction and by enhancing proximal reabsorption.[1,3] This notion was based upon the observation that replacement of salt and water losses would prevent hyperuricemia.[20] However, since the reabsorptive capacity is normally much greater than the filtered load of uric acid, it is difficult to see how further increasing proximal reabsorption could cause hyperuricemia. It seems more likely that thiazide drugs affect either the secretory process or the postsecretory reabsorptive

TABLE 3.—*Possible Sites of Action of Thiazide Diuretic Drugs*

Proximal Reabsorptive Site
Secretory Site
May blunt secretion, suggested by failure of C_{urate}/C_{inulin} to increase as serum urate is increased
Postsecretory Reabsorptive Site
Analogous to the increased Ca^{++} reabsorption (relative to Na^{+}) which is also seen with thiazide drugs



SK&F 62698 (ANP 3624)

[2,3-dichloro-4-(2-thienyl-carbonyl)phenoxy] acetic acid

Figure 1.—Structural formula for ticrynafen (tienilic acid, Selacryn®). (Reproduced with permission from Okun and Beg.[26])

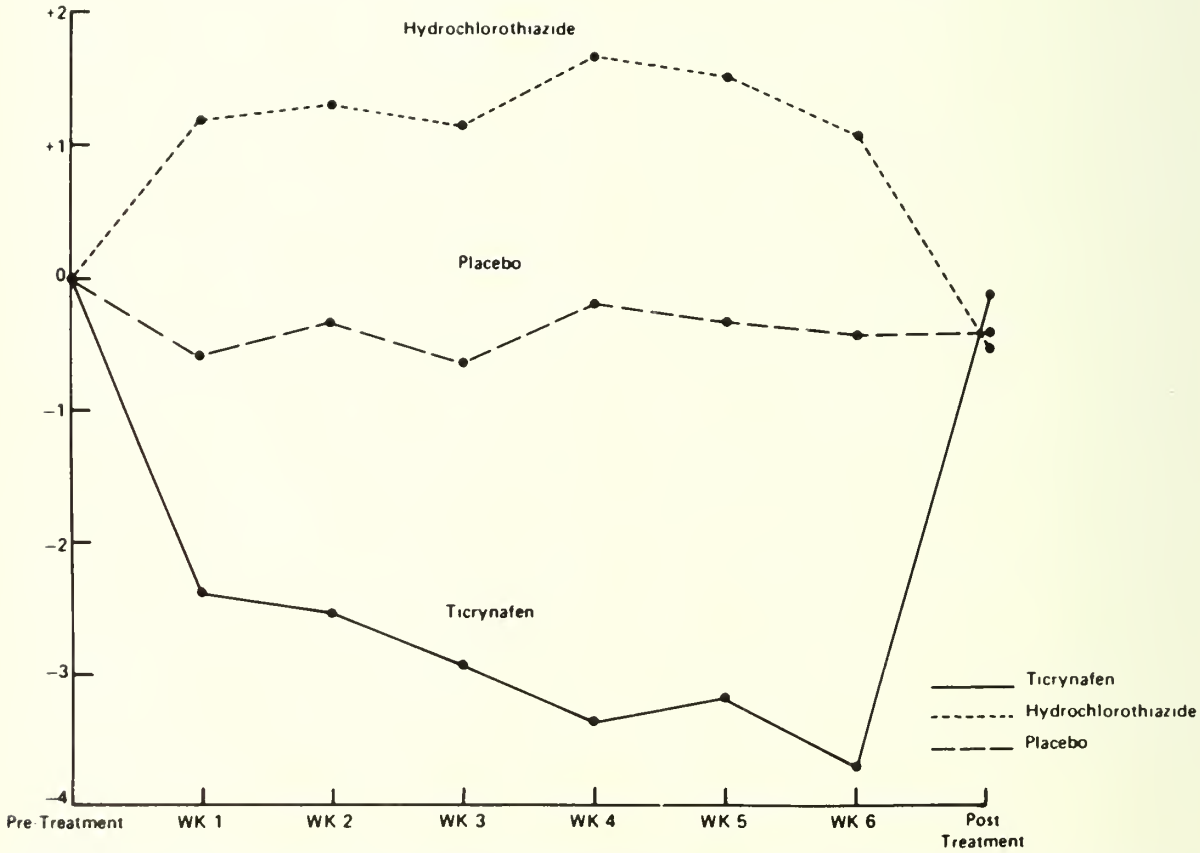


Figure 2.—Changes in serum uric acid. Mean pretreatment values (mg per dl): ticrynafen, 6.3; hydrochlorothiazide, 6.9; placebo, 7.7. (Reproduced with permission from Okun and Beg.[26])

process (Table 3). Blunting of the normal increase in the urate secretion rate together with increased levels of serum uric acid suggest that thiazide drugs affect the secretory process.[17] The postsecretory reabsorptive site is another possible site of action of thiazide drugs. This effect may be analogous to the increase in distal calcium reabsorption relative to sodium reabsorption seen with these diuretic drugs. Blunted secretion or enhanced distal reabsorption would result in an increase in the level of serum uric acid.

A new diuretic drug will shortly become available. Its structural formula is shown in Figure 1. This agent is called tienilic acid in Europe and ticrynafen in the United States (it will be marketed as Selacryn® by Smith Kline & French Laboratories). It is chemically related to ethacrynic acid, but it is not a potent loop diuretic. The renal effects of this drug are nearly identical to thiazide diuretic drugs with one important exception.[21-26] Okun and Beg[26] examined levels of serum uric acid in patients who were treated for six weeks with either hydrochlorothiazide, ticrynafen or placebo (Figure 2). The dotted, upper line shows the results of hydrochlorothiazide treatment, and after six weeks the level of serum uric acid increased nearly 2 mg per dl in these patients. In contrast, the solid, lower line represents a very dramatic fall in the levels of serum uric acid in patients who had received ticrynafen. This fall in the level of serum uric acid with ticrynafen is acutely associated with an increase in uric acid excretion. When compared to thiazides, ticrynafen has also been shown to be an adequate diuretic drug for treating hypertension, at least in short-term crossover studies.[24-26] It may be rational to use this drug in patients with worrisome hyperuricemia, but I should like to emphasize in closing that the worry is more in the mind of the physician than in the patient with asymptomatic hyperuricemia.

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Important Advances in Clinical Medicine

Epitomes of Progress—Nuclear Medicine

The Scientific Board of the California Medical Association presents the following inventory of items of progress in nuclear medicine. Each item, in the judgment of panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in nuclear medicine which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Nuclear Medicine of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Gallium Imaging—Is It Useful?

THE USE OF gallium 67 citrate in tumor evaluation and in the detection of occult infection has become an accepted clinical procedure. However, in both uses the efficacy and accuracy of the procedure depends on several factors. Histology, vascularity and anatomic site are of importance in the evaluation of tumors. When used for the detection of infection, the location, amount of leukocyte labeling and leukocyte migration to the inflammatory site influence the degree of uptake.

The malignancies in which gallium 67 citrate has been helpful in staging and in the clinical follow-up of postradiation therapy and chemotherapy include the following: Hodgkin and non-Hodgkin lymphoma, hepatoma, bronchogenic carcinoma, and testicular tumors particularly seminomas. It is of questionable value in most adenocarcinomas including breast, prostate, and gastrointestinal tract tumors. Because of the significant normal gallium 67 concentration within the colon, studies are most accurate when limited to the thorax. When used in a selected patient population, the accuracy of the procedure approaches 90 percent to 95 percent.

In the appropriate clinical situation, gallium 67 is useful in the detection of occult infection and a few nonmalignant lung conditions. Combined bone and gallium imaging is helpful in the initial evaluation of osteomyelitis and in the follow-up of therapeutic results. The bone image will remain positive long after the gallium 67 image has returned to normal since the latter is indicative of acute infection. Abscess detection, particularly in the abdomen, is difficult but if the gallium 67 image is negative it is unlikely that an inflammatory process is present. Renal and perirenal infection can be satisfactorily evaluated by gallium 67 imaging because under normal conditions there should be no gallium 67 concentration in the kidneys after 24 hours. Additional uses of gallium 67 imaging that are now proving to be beneficial include the study of chemotherapy lung toxicity, sarcoidosis and pneumoconiosis.

JUDITH ROSE, MD
WILLIAM BLAHD, MD

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Gallium and Bone Scanning to Monitor Response to Therapy in Chronic Osteomyelitis

CHRONIC OSTEMYELITIS is an unpredictable disease which is difficult to control and treat. Aside from the clinical response and well-being of the patient, radiographs have traditionally been used to follow the course of patients with osteomyelitis. The bone scan using technetium 99m labeled phosphate compounds has been shown to be a very sensitive procedure for detecting abnormalities of bone which affect bone blood flow or bone turnover. The gallium scan, although originally examined as a potential bone scanning agent, is clearly an unsatisfactory radionuclide agent for bone evaluation, except in the case of osteomyelitis.

Nuclear imaging is carried out with technetium polyphosphate or pyrophosphate, diphosphonate, or methylene diphosphonate, with imaging on the scintillation camera two to three hours after the intravenous injection of 15 mCi. The gallium scan is done with 5 mCi of gallium 67 citrate, injected intravenously, followed by imaging 72 hours after injection on the scintillation camera or scanning instrument. These nuclear imaging procedures may be recorded on a computer disk and analyzed to obtain quantitative data on the degree of uptake in the lesions relative to normal bone uptake in the opposite extremity.

In a study involving 14 patients with chronic osteomyelitis, who were followed over a one-to-two-year period by clinical, radiographic and nuclear techniques to evaluate response to antibiotic therapies, nuclear techniques were far more sensitive to the patients' response to therapy than were radiographs. In fact, in almost all cases the radiographs showed no change, despite pronounced changes in nuclear images and clinical patient response.

The results of this study were that four of the 14 patients had positive clinical response to antibiotic therapy, seven of 14 had no response and two had partial response. The technetium phosphate images agreed with clinical response in all except one patient where the phosphate images continued to be notably abnormal even though there was clinical response in the patient. Gallium images agreed completely with the clinical response in all cases, including one in which the phosphate scan did not agree. Radiography showed no substantial change over the course of therapy in those patients studied.

In summary, gallium scans and bone scans both show a sensitivity for following the course of patients with chronic osteomyelitis. Without doubt, the results of the study described indicate that the sensitivity of the scans is superior to that of x-ray examination for evaluating in these patients.

NAOMI ALAZRAKI, MD

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The Exercise Heart Function Test

A NOT UNCOMMON PROBLEM in clinical practice are those patients who present with a positive stress electrocardiogram (ECG) without symptoms and with chest pain atypical for angina, an abnormal but nonspecific resting ECG, a strong family history, or other findings that are suggestive but not diagnostic of coronary artery disease. Cardiac catheterization is not indicated in many of these cases because of the high percentage of normal coronary arteries that will be found.

The nuclear exercise heart function study is proving to be useful in the evaluation of such patients. In this test a radiopharmaceutical which acts as a blood pool imaging agent (such as technetium 99m tagged to human serum albumin) is injected intravenously and the left ventricle is imaged with a standard gamma camera with the patient at rest and then during a period of supine bicycle exercise. Computer analysis allows the sequential calculation of the left ventricular ejection fraction (LVEF), an index of heart function and a visual assessment of regional wall motion.

Borer and co-workers were among the first to show that normally the LVEF increases with maximum exercise but falls in the case of coronary disease. Work in our laboratory has shown that LVEF in asymptomatic patients with coronary artery disease tends to remain unchanged with peak exercise. The sensitivity of this test appears high (95 percent), although other causes of left ventricular dysfunction with exercise such as cardiomyopathies must also be ruled out. An occasional patient with single vessel right coron-

ary artery disease may have a normal response, but it is clear that this test is considerably more sensitive than standard ECG treadmill testing for the detection of hemodynamically significant coronary artery disease.

DONALD GORDON, MD

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Radionuclide Bone Imaging in Stress Fractures

WITH THE PRESENT INTEREST in physical fitness the incidence of stress fractures has increased. Pain, heat and swelling may occur acutely, or insidiously, without a direct association with stress. The differential diagnosis may include cellulitis, thrombophlebitis, tendonitis, malignancy, inflammation, soft tissue injury hematoma, osteosarcoma or osteomyelitis. Radiographic diagnosis may be difficult. Bone images, which reflect osteoblastic activity and blood flow, are useful in these instances, as well as in fractures of radiographically difficult bones, such as ribs, metacarpals, carpals, metatarsals, tarsals, and skull and scapula.

Stress fractures start with bone resorption during the 48 to 72 hours after stress, followed by bone remodeling, which lasts two to three weeks. When resorption is greater than replacement, the cortex is weakened and fractures may result. They are common in the femoral neck (where they may progress to an overt fracture with displacement), the tibia (usually the plateau), metatarsals, os calcis, distal femoral diaphysis and pubic rami. The treatment is rest.

A standard bone image is obtained: 10 mCi of technetium 99m diphosphonate, or a similar agent, is given intravenously. Imaging is done one to three hours later. In acute injuries the image may be negative for 24 to 48 hours, while there is vasoconstriction and discontinuity of osseous circulation. However, in one study findings were positive in 24 of 28 stress fractures during the first 24 hours. These early abnormal findings are seen in young patients, in incomplete or well-approximated fractures and in smaller bones. The abnormal image is delayed in elderly patients, if there is poor approximation or immobilization, and where there is a compromised blood supply, previous irradiation or an underlying bone abnormality such as osteoporosis.

Radionuclide images may be positive before an actual fracture occurs, explaining the observation that in patients with positive tibial plateau images who were given rest, abnormal findings never occurred on radiographs.

Bone images are useful in the diagnosis of occult fractures or those occurring in bones that are difficult to diagnose radiographically.

NANCY TELFER, MD

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Emergency Nuclear Medicine Procedures

TO MEET THE DEMAND for emergency nuclear medicine procedures, those studies whose results have an immediate effect on the patient's care have increased significantly in many laboratories. The immediate availability of technetium 99m labeled agents and improved and portable imaging cameras help provide needed information rapidly.

About half of the emergency procedures are lung perfusion studies to rule out pulmonary embolism. Abnormal studies may be further evaluated by ventilation or aerosol imaging or by angiography. A normal perfusion scan done in at least four views virtually rules out pulmonary emboli.

About 25 percent of emergency procedures are liver-spleen studies for abdominal trauma associated with a falling hematocrit, where ruptured or lacerated organs are suspected. Four or five spleen views are necessary to look for filling defects or irregular margins. In doubtful cases repeat studies may show persistence, enlargement or disappearance of the defect. Standard liver studies are also done to rule out amebic or purulent abscesses.

Occult abscesses may be evident on a four-hour gallium-67 study. In questionable cases, a 24-hour or 48-hour image must be obtained. Pneumonias may be evident as a region of increased uptake even before an x-ray study of the chest shows abnormalities.

Other emergency nuclear studies include static brain imaging to rule out abscesses or other space occupying lesions before spinal tap. Possible kidney trauma may be evaluated by technetium 99m glucoheptonate imaging on an emergency basis. Bone scanning may be helpful to evaluate the hips for possible infection because failure to recognize and institute surgical draining may result in necrosis of the femoral head.

NANCY TELFER, MD

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Iodine 125 Fibrinogen Uptake Test

THROMBOPHLEBITIS occurs in several million persons every year in the United States and emboli occur in 10 percent of these persons. Although more likely to occur in patients in hospital, thromboembolic disease also occurs in otherwise healthy persons. Less than 50 percent of patients with thrombophlebitis have significant clinical manifestations, and in only 35 percent of patients is a presumptive diagnosis of thrombophlebitis corroborated by diagnostic procedures. Diagnostic advances have led to a better understanding of this disease and to improved methods for its diagnosis. Although radiopaque venography is at present the "gold standard," it is not suitable for screening because of its complexity, invasiveness and risk of induction of thrombophlebitis (5 percent to 15 percent). Standard laboratory blood tests are inadequate although newer radioimmunoassays have substantial promise. Radiopaque venography shows four cardinal signs of thrombophlebitis: (1) constant filling defects, (2) abrupt termination of the contrast column, (3) nonfilling of the entire deep venous system or portions thereof and (4) diversion of flow into collateral veins.

The ^{125}I fibrinogen uptake test, now generally available in the United States, is suitable for general screening purposes, and a diagnosis can be confirmed within four to 24 hours after administration of the radiopharmaceutical. When homologous fibrinogen is labeled with radioactive iodine and injected, it behaves like the patient's own fibrinogen. When a thrombus forms, fibrin, including some of the labeled fibrinogen is deposited, so that the thrombus will have a higher concentration of radioactivity than the surrounding areas. The ^{125}I fibrinogen uptake test is only positive when fibrin is actively deposited; therefore old or well established thrombi may be missed. In practice, this has not proven to be a major problem; experimental evidence suggests there is dynamic exchange of fibrinogen between the blood and established thrombi. Emissions from the radioactive iodine are detected by external counting over the veins; a clot is localized by radioactive counts in excess of background counts of tagged fibrinogen in the circulating blood. Counts may be taken at the bedside by a technician using a lightweight, hand-held scintillation detector. The legs are counted in segments extending from the inguinal ligament and following the course of the femoral vein to the posterior aspect of the knee, then to a point just posterior to the internal malleolus of the ankle. Counts are done once or twice on the day of injection and daily thereafter until the test becomes positive. If there are indications of a thrombus, then counting can be continued to observe whether the thrombus is extending or dissolving, or to assess the effect of therapy. A difference in uptake when compared with (1) the same site on the opposite leg or (2) adjacent sites or (3) earlier uptake over the same site is interpreted as evidence of thrombophlebitis.

Clinical studies have documented the efficacy of the ^{125}I fibrinogen uptake test for diagnostic use in patients with established thrombophlebitis, as well as for prospective use in patients in whom there is risk of thrombophlebitis developing. The test is positive in two thirds of patients with existing thrombophlebitis by 3 to 4 hours and in almost all others by 24 hours after injection of the fibrinogen. There are virtually no adverse effects. When compared with radiopaque venography, it has a sensitivity of 90 percent and a similar specificity if certain well-defined conditions are considered. Other inflammatory diseases may also cause a positive result. It is particularly important to search for conditions (ulcers, hema-

toma, arthritis, fractures, gross edema) and procedures (injections and surgical operations) which can give rise to positive results because of fibrinous deposition. A positive scan and a negative venogram may be indicative of a falsely negative venogram, particularly in the calf. The ^{125}I fibrinogen uptake test is less satisfactory in the upper thigh and the pelvic area. However, 80 percent of thrombi in the legs originate or are associated with calf thrombi. Patients who have local problems, such as those who have had total hip replacement, may be exceptions. Radiopaque venography may be necessary to resolve difficult diagnostic problems.

GERALD L. DeNARDO, MD
SALLY J. DeNARDO, MD

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Gallium 67 Citrate in Hepatoma of the Liver

CIRRHOSIS OF THE LIVER as a sequela of alcoholism is encountered almost daily by physicians specializing in primary care. Management of this condition primarily involves encouragement in the abstinence from alcohol and in proper nutritional maintenance, as well as persistent vigilance for appearance of complications of cirrhosis such as esophageal varices, hepatic encephalopathy, ascites and the like. Perhaps less common, but certainly of considerable importance due to its lethal nature, is the development of hepatoma in the cirrhotic liver.

At present, the commonly available specific screening tests for hepatoma are limited to the assay of serum alpha-fetoprotein and hepatic scintigraphy. When positive, the alpha-fetoprotein assay is an excellent indicator of the presence of hepatoma and is a valuable adjunct for evaluating response to therapy. Unfortunately, alpha-fetoprotein has been found to be negative in up to 50 percent of proven cases of hepatoma.

Liver scintigraphy in cirrhosis is routinely done with technetium 99m sulfur colloid. The findings in cirrhosis are usually characteristic and invariably show some degree of mottling of the liver, increased splenic size and concentration of the nuclide, and appearance of the nuclide in the bone marrow. Ascites, if present, is suggested by a separation between the liver and the ribs which usually contain increased nuclide in the marrow.

The mottled pattern of nuclide distribution within the liver varies from minimal to severe and, at times, appears as focal defects. These defects are areas devoid of Kupffer cells secondary to the fibrosis and regenerating nodules of hepatocytes characteristic of cirrhosis. Unfortunately, these areas of mottling often cannot be differentiated from other lesions within the liver such as metastatic carcinoma, hepatoma or abscess.

Gallium 67 citrate has been shown to be avidly concentrated in greater than 90 percent of hepatomas. In fact, hepatoma appears to be one of the few solid lesions that concentrate ^{67}Ga citrate more than does normal liver tissue. Therefore, in a patient with cirrhosis who has a "cold" lesion on ^{99m}Tc Sc, which concentrates ^{67}Ga more intensely than the surrounding liver tissue, a presumptive diagnosis of hepatoma can be made. Certainly such lesions as abscesses and occasional metastatic tumors can give similar findings. However, the absence of clinical findings suggesting infection, or an ultrasound study of the liver showing the lesion to be solid, effectively excludes an abscess from consideration. In addition, the lack of an apparent focus of another primary tumor limits the likelihood of a metastatic etiology.

In our institutions during the past year, seven cases of histologically proven hepatoma were imaged with ^{67}Ga. In each case, the "cold" area in the liver on ^{99m}Tc Sc imaging filled in intensely with ^{67}Ga. There were no instances in which a hepatoma was incorrectly diagnosed by the ^{67}Ga scan. In none of these cases was the ultrasound study able to define a characteristic tumor pattern. Ultrasound did, however, effectively eliminate abscess as a consideration.

A ^{67}Ga citrate scan of the liver in a patient with cirrhosis showing uptake in a "cold" lesion on a ^{99m}Tc liver scan greater than the uptake in the surrounding liver is a highly sensitive indicator of hepatoma.

RICHARD WILLIAMS, MD

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Patient Selection for Thallium 201 Myocardial Imaging With Exercise Stress

EVEN WITH TODAY'S sophisticated medical technology, the history and physical examination remain essential in patient management. The selection of patients for thallium 201 myocardial perfusion imaging with exercise stress is a good example of this principle.

The sensitivity of this test for coronary artery disease is approximately 70 percent which is about the same as for electrocardiographic (ECG) exercise stress testing. The specificity, however, is significantly higher (96 percent) as compared with ECG stress testing (87 percent), resulting in fewer false positive results with the radioisotope procedure.

Careful patient selection is necessary in order to obtain maximum benefits from the test results. Such selection involves the clinical estimation of the pretest probability of the patient having coronary artery disease. If this probability is judged to be high, such as in a patient with typical angina pectoris, a positive myocardial perfusion exercise test contributes little and a negative test may be seriously misleading. In general, the test becomes more valuable in cases where the pretest probabilty is low, such as in a young asymptomatic person in whom findings on ECG stress testing are positive, or a patient with chest pain quite atypical for coronary artery disease. Atypical chest pain which is highly suspicious for ischemic heart disease has been advocated as another indication for the test, but not all authorities agree, arguing that the probability of coronary artery disease in the face of a negative test is too high to forgo further diagnostic evaluation. The pretest clinical evaluation of a patient, therefore, may help decide (1) whether the test is in fact needed and (2) the predictive value of the test, particularly if findings are negative.

DONALD GORDON, MD

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ADVISORY PANEL TO THE SECTION ON NUCLEAR MEDICINE

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San Francisco

EDITORIALS

A Needed Next Step in Health Care

A Lesson From Nature?

In spite of all the bluster and rhetoric in high places it appears that national health insurance in the form of a nationalized health care system is now a dead issue for practical purposes. And the reason is simple enough. It has finally become evident that medical and health care, plus the paraphernalia of yet another huge federal bureaucracy with its attendant cumbersome and costly regulations, will certainly cost more than the nation is able or willing to pay at this time and probably in the foreseeable future. This is quite different from the situation that has existed for the past several decades which has been characterized by a more or less continuing power struggle for and against socialized or government medical care. Nationalized medicine on the British model has now become most unlikely for America. It may, therefore, be time to reassess the power struggle which has gone on for so long and to regroup the energies of all concerned.

The present situation would appear to be the result of long-standing efforts to solve things by the use of power. At best there has been indifferent success from anyone's standpoint. This may be at least partly because power in both government and in the private sector is so divided. In government it is divided among the legislative, executive and judicial branches, and among local, state and national objectives and interests. In the private sector it is divided among medicine (which is even divided within itself), other segments of the health professions and what is often referred to as the health care industry. And then in the last few years there have been attempts to give power to the people through the consumer and often minority dominated Comprehensive Health Planning and, more recently, the Health Services Agencies. The result of all this has been somewhat of a standoff with no one's objectives being accomplished in spite of the expenditure of an enormous amount of time, energy and dollars by all concerned.

Perhaps the time has come to turn from emphasis on confrontation among adversaries toward a greater emphasis on efforts at collaboration. As it is now, all segments are more or less organized for survival and enhancement of power (and not the least among these are the governmental bureaucracies), when what is needed is some genuine cooperation and common effort to get a job done. It would seem that there is indeed a clear need and opportunity to shift from confrontation to cooperation at this time and obviously this will require a new spirit and a new approach.

It should perhaps be noted that the process of organizing as things get more complex (as they surely have done in health care) is a natural phenomenon. As Teilhard is said to have pointed out, matter itself tends to become organized into ever increasingly organized systems and interrelations of systems when observed over long periods. This becomes more easily recognized when it reaches the molecular and cellular levels of biology, and it certainly happens in human affairs as well. In each case it seems to occur when there is a need to achieve a more efficient use of energy in performing a needed function. It is therefore suggested that a needed next step in health care is to overcome the habit of confrontation, which has dissipated so much of time, energy and dollars, without really accomplishing anyone's objectives, and move on toward the higher levels of cooperation and collaboration which will be necessary if the complex technologic, social, economic and political problems

of medicine and health care are ever to be dealt with efficiently or effectively.

This is a challenge to our leadership in both the public and private sectors—whether at the local, state or national levels. It seems unlikely that much will be accomplished until there is a new approach. If there is a lesson from nature, or a model from nature, it would seem that collaboration and cooperation with efficient use of energy and resources and each contributing to the success of the whole is the key. This will require a number of relatively autonomous sources of power, not only in government and in the organizations and institutions of the private section but perhaps even including physicians, patients and individual citizens, to pull together in a spirit of good will and direct their energies and resources to the accomplishment of agreed upon solutions to agreed upon problems in the common interest of all.

This appears to be a needed next step in health care—and there could be a lesson in nature.

—MSMW

Of Sleep and Seals and Many Things: Pickwickians—1978

THE REVIEW by Morgan and Zwillich elsewhere in this issue provides a lively and timely summary of the problems of hypoventilation in the obese, especially during sleep. Their review stands on its own and this editorial will emphasize some additional nuances not covered in the review and will consider nosology and human culture, an animal model, pathogenesis, the heart in obese persons and therapy.

Nosology and Human Culture

The choice of the term obesity-hypoventilation syndrome (OHS) is logical, but it has limitations. It is not as appealing, culturally, as the term Pickwickian syndrome. Medicine needs all the ties to the broad stream of human culture that it can develop. OHS deprives Charles Dickens of the priority that is correctly his. Whether Joe the Fat Boy was derived from Dickens' imagination or was originally a real-life person is immaterial. Dickens' description is still the single most accurate description and is marvelously fashioned as well. OHS does not emphasize the pathologic somnolence and appetite found in many of the patients which usually persist despite loss of weight. As a result, OHS is a less complete and satisfactory designation.

The Seal as an Animal Model

Knowledge of the syndrome has been handicapped by lack of an appropriate animal model. An animal model may now be available. Professor Kooyman of the Scripps Oceanographic Institute has recently studied ventilation and blood gases during sleep in Weddell seals. This aquatic mammal is certainly obese. An adult weighs about 1,500 pounds, much of which is blubber. To maintain this body mass, Weddell seals must have substantial hyperphagia. Seals generally have depressed respiratory centers while awake, presumably as an adaptation which subserves prolonged diving. Seals are polycythemic to a pronounced degree, like human Pickwickians. While sleeping on the ice floes of their native Antarctica, Weddell seals develop apnea of seven to eight minutes duration. When the animal awakes, apnea is abolished. During seal sleep apnea, arterial oxygen pressure (Pa_{O_2}) drops to as low as 20 torr; arterial carbon dioxide pressure (Pa_{CO_2}) rises only to about 50 to 60 torr (mm of mercury) (J. Kooyman—personal communication). This indicates that as in human Pickwickians, sleep is associated with altered ventilation-perfusion abnormalities as well as accentuated respiratory depression and alveolar hypoventilation. Quickly after waking, blood gas values return to normal.

One interesting sidelight of this comparative model relates to the relation between substrate utilization and the control of breathing. In human Pickwickians but not in normal persons, hypocaloric ketogenic diets significantly increase the respiratory response to carbon dioxide. This improvement correlates with ketone body concentrations and dietary manipulation leading to ketosis and has been suggested as a possible therapeutic manipulation.[1] This might represent an additional mechanism by which weight reduction improves Pickwickians, independent of a direct effect on

pulmonary mechanics. Seals often subsist for long periods on endogenous substrate (starvation); however, without the development of significant ketosis.[2] Thus seals may be especially appropriate for pursuing this fascinating metabolic aspect of depressed respiratory control in Pickwickians.

Pathogenesis

It is now generally accepted that Pickwickians represent a subset of a larger group of patients with sleep apnea. This subset is made up of patients with massive obesity, alveolar hypoventilation awake and accentuated during sleep, with reversal of alveolar hypoventilation with simple weight reduction. It is conventional to classify sleep apnea into three groups: (1) patients with upper airway obstruction during sleep (obstructive type) in which apnea results from obstruction of upper airways during sleep because of neurologic abnormalities, or occasionally because of structural lesions of the airways, (2) patients with pure depression of the respiratory center which is accentuated during sleep (central type) and (3) mixed sleep apnea (both obstructive and respiratory center depression present). It appears that most Pickwickians represent a combination of depressed central respiratory drive and mechanical and blood gas abnormalities caused by obesity.

The major gap in this theory of pathogenesis is that neither nervous system structural lesions nor precise neurophysiological abnormalities have been reported in Pickwickians or in many patients with sleep apnea. Therefore, the evidence provided in the review for either central depression or carotid body depression is indirect. This critical deficiency will not be remedied until precise neurophysiological techniques are applied to these patients. Studies based on peripheral changes (ventilation, gas exchange) can provide only indirect evidence. As recently *quoted by* an eminent neurophysiologist:

> Fundamentally the control of ventilation is neuronal in nature. Therefore, ventilatory control must ultimately be described in acceptable neurophysiologic terms.
>
> Because of the diverse connections, the problem of determining mechanisms of abnormal ventilatory control is quite complex. Given an abnormality in ventilatory response, the abnormality may reside in any segment of the total neuronal connections subserving a given function. For example, a blunted hypoxemic drive could arise from direct abnormality of the carotid body itself; from changes in arrival time in afferent nerves; from increased inhibitory stimuli or decreased activating stimuli from a variety of central neurons, or from inadequacy of the peripheral ventilatory mechanism.
>
> Classic approaches to the study of ventilatory control, say during exercise, which measure variables based on effect or function such as ventilatory volume or gas exchange parameters, must be cautiously interpreted. At the very least, these studies will require reinterpretation in neurophysiologic terms.[3]

In furthering such neurophysiologic studies, the use of seals as animal models might be particularly useful.

The Heart

Abnormalities of cardiac function frequently play an important role in Pickwickians. Charles Dickens described Joe the Fat Boy as "young Mr. Dropsy." His edema may have been related to cor pulmonale (although venous insufficiency of the obese cannot be excluded as the cause). Pickwickians commonly show reversible pulmonary hypertension and right ventricular failure. Alexander and co-workers showed that massively obese patients, even in the absence of alveolar hypoventilation, showed impairment of left ventricular function.[4] This was attributed to the increased volume work of the left ventricle because of the increased blood flow required by excess fat. Tilkian and associates showed severe intermittent pulmonary hypertension and a substantial incidence of bradyarrhythmias and tachyarrhythmias during episodes of obstruction in obstructive sleep apnea.[5] Thus careful evaluation and management of cardiac factors is an important aspect of patient management.

Therapy

Morgan and Zwillich suggest an aggressive approach, especially in obese patients with obstructive sleep apnea associated with serious bradyarrhythmias and tachyarrhythmias and profound desaturation which is life-threatening. The difficulty is in defining life-threatening. Two important aphorisms may be worth remembering: (1) Not all that snores is obstructive sleep apnea and (2) if you tracheostomize in a hurry, the patient may repent in leisure. Sleep apnea has been so widely publicized in the medical and lay press that large numbers of patients, often obese and almost invariably snorers, are referred to hospitals for "definitive" therapy (tracheostomy). A number of these patients do not, in fact, have clinically important sleep apnea and will not be benefited by tracheostomy. Documenting signifi-

cant upper airway obstruction and relief by intubation should be a precondition before surgical operation is undertaken. Careful physiologic measurements during sleep and a trial of weight reduction together with measurements following reversible airway intubation should precede tracheostomy. A careful search for anatomical causes of upper airway obstruction should be conducted. For example, in young patients, tonsillar-adenoid obstruction should be specifically investigated. In adults, upper airway tumors should be ruled out. It is necessary to emphasize the fact that in central sleep apnea, tracheostomy is contraindicated.

Aside from weight reduction, either long-term or intermittent (patients with pathologic hyperphagia find long-term dieting intolerable), progestational drugs have been recommended. No careful clinical trial of these has been done, but their use entails relatively low toxicity and this form of therapy is at least logical in patients with almost pure "central" alveolar hypoventilation.

Summary

Joe the Fat Boy was described by Dickens in 1837. The first scientific description was provided by Sieker and associates in 1953. The Pickwickian name was first applied and the role of alveolar hypoventilation, central respiratory depression, and the independent nature of hypersomnolence and hyperphagia were first described by Burwell and co-workers in 1956. Since then, as indicated in the review, substantial information has been accumulated. As indicated in this editorial, much, however, remains to be learned and therapy continues to be pragmatic and anecdotally based. In similar fashion, the operation of disease, during the third of our lives that we spend sleeping, is not well understood.

EUGENE D. ROBIN, MD
Departments of Medicine and Physiology
Stanford University School of Medicine
Stanford, California

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Plague on Us

SINCE ANCIENT TIMES bubonic plague has been the subject of intense dread, a rich stimulus for literature and at times a major influence on the course of history.[1] Characteristically, the disease has occurred in cycles with major pandemics at irregular intervals and with intervening epidemics in various parts of the world. Over the past 1,500 years, four plague pandemics have been documented. The first was recorded in the sixth century AD, beginning in Egypt, speading to Constantinople and then to Europe and persisting for about 60 years. The second occurred in the 14th century and was carried from Asia Minor and Africa to Europe by merchants and other travelers, where, known as the Black Death, it decimated the population. It is estimated that millions died in Asia, and in Europe. About a fourth of the population—at least 25 million people—fell victim to the pestilence. The third pandemic, again involving Europe, occurred during the period of the 15th to 18th centuries, finally subsiding to be succeeded by the fourth pandemic, beginning in China about 1860 and continuing to the present.

That plague is still with us, even in the United States, is effectively illustrated in the case presented and discussed by Connor and associates in the Speciality Conference elsewhere in this issue. The case was that of a 3-year-old child who became ill while vacationing with her family at California's Lake Tahoe. The family returned home to San Diego where, despite rapid diagnosis and appropriate therapy, the child died—the only fatality and the only recorded case of plague in San Diego.

The California "connection" in this case is of interest because California figured prominently in the importation of the disease into the United States during the worldwide pandemic still in progress.[2] Although apparently reemerging in the Chinese province of Yunnan in about 1860, the disease attracted worldwide concern in 1894 when it reached Hong Kong.[3] The means for rapid widespread transmission was now at hand through extensive ocean commerce, and by 1899 it had reached the Americas with the first New World case in Santos, Brazil. The plague bacillus, Yersinia pestis, had been identified by Yersin in 1894. (Yersin's contribution was recognized recently by changing the name of the genus from

Pasteurella to Yersinia.) Although it is likely that the plague bacillus was introduced at about the same time into the United States ports of San Francisco, New Orleans and New York sometime after 1894, the Black Death was first recognized in San Francisco on March 6, 1900.[2] Conditions in San Francisco at that time—rapidly expanding industry, booming commercial and tourist trade, the crowded slums of Chinatown, the prevalent distrust of the Chinese population for Western medicine and culture, and a nexus of political, commercial and governmental interests—all combined to produce one of the most fascinating and scandalous episodes in American medical history. The result was a study in *denial*. The press, the governor, the state board of health, the Chinese and all but one of the local newspapers stubbornly insisted that plague could not exist in San Francisco. It was bad for business.[1] Lined up on the other side were the mayor, the city board of health and the federal health authorities. A special commission was formed, and racial prejudice in high government office uncovered. It seems possible that the initial failure to take definitive action may have facilitated dissemination of the disease in the West.[2] Some two years after the commission of plague experts had definitely declared that plague existed in San Francisco, the state government finally admitted that the disease might be present. Eventually, after significant reform, a strong state department of public health emerged along with increased public awareness of the dangers of communicable diseases.

Subsequent epidemics of plague occurred in California in 1906, 1919 and in 1924, when the last United States outbreak of pneumonic plague resulted in 30 fatalities in Los Angeles. Since that time, over the last 50 years, all United States cases of human plague have stemmed from individual contacts with the wild rodent population which comprises the sylvatic cycle.

Plague is now firmly entrenched as an enzootic infection in a variety of rodent species in the dozen states extending from California to Texas, and from Montana to New Mexico. During the last decade, sporadic human cases have occurred mainly in New Mexico, Arizona, California, Colorado and Oregon. Human cases occur in a cycle which peaks about every five years.[4] Significantly, the annual number of cases in the United States has been higher in the 1975-1977 period than at any time in the previous 50 years. The usual recognition of 2 to 5 cases per year increased to 20 in 1975, 16 in 1976, and 18 in 1977. Early indications suggest that the annual rate is again declining at present.[5] The five year periodicity likely reflects some as yet poorly understood cycle in the wild animal reservoir.

Although there is reason to believe that the case fatality rate in bubonic plague cases treated early should be less than 5 percent, it is nevertheless true that the mortality rate in the sporadic cases in the United States averaged 21 percent over the 1950-1975 period and was still 19 percent in 1976. As with other relatively uncommon and focally occurring diseases such as Rocky Mountain Spotted Fever (now much more common on the Atlantic Seaboard than in the Rockies), optimum outcome depends upon early recognition and prompt initiation of appropriate therapy. Public awareness and a high index of suspicion by physicians are thus essential for effective diagnosis and management. Increased awareness of plague in recent years along with increased potential exposure for larger numbers of Americans has been one of the consequences of the Vietnam conflict, since human plague is endemic in South Vietnam, especially among the primitive Montagnard tribesmen.[6] The extremely low incidence of plague in Americans in South Vietnam in the 1966-1971 period, despite concomitant epidemics in the civilian population, suggests that the available plague vaccine is highly protective.[7] Current indications for the plague vaccine have recently been defined.[8]

The San Diego case presented and discussed in this issue illustrates a number of important aspects of the disease at this time. Among the significant points brought out by Connor and associates are the following: three fourths of United States cases are occurring in young persons (under age 25); 95 percent of cases present with a single enlarged lymph node. Immediate needle aspiration of the node should be carried out under antibiotic coverage for diagnosis. Although virtually all cases in the United States since 1924 have apparently resulted from incidental involvement of man in the sylvatic cycle (that is, contact with the enzootic wild animal reservoir), nevertheless there still is a real potential for development of a murine cycle in domestic rats (with resultant implications for the development of epidemics in humans), as evidenced by the

finding of infection in domestic rodents in Denver as recently as 1968. Recently, sick domestic cats and other carnivores have been implicated in human cases. (Unfortunately, sylvatic plague in the wild animal reservoir appears almost impossible to eradicate at present.) Finally, effective laboratory techniques are now available, especially in Public Health Department laboratories, to assist in confirmation of the diagnosis. Again, however, a high index of clinical suspicion, consideration of epidemiological factors and prompt initiation of therapy are essential for a favorable outcome.

JOSEPH E. JOHNSON III, MD
Professor and Chairman
Department of Medicine
The Bowman Gray School of Medicine of Wake Forest University
Winston-Salem, North Carolina

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Lessons from the Nork (Gonzales) Case

In a special article elsewhere in this issue Judge B. Abbott Goldberg recounts with clarity the evolution in medicine, and in the law, of the responsibility and duty of hospitals and medical staffs to regulate the quality of patient care. He briefly reviews the past and his own direct experience with the present, gives a glimpse into what may be in store for the future and then politely hints that the law will likely follow medicine if medicine will show the way.

Both the law and medicine can support the premise that the regulation or assurance of quality in patient care is for the safety and benefit of patients. But as patient care has at once become more effective and also more dangerous, neither the law nor medicine has yet developed adequate mechanisms to detect and eradicate incompetence and do this promptly and with fairness. At present there are many difficulties. Each profession approaches the problem from a different frame of reference; one seeking to punish or eliminate incompetence and the other to enhance excellence; one seeking to regulate and the other to assure; and one refers to the recent, well-publicized case as Gonzales and the other as Nork. And because of differences in approach the two systems tend to address the problems of quality in patient care more often as adversaries than as collaborators in the patient and public interest.

The problems of regulating or assuring quality in patient care are real, as are the difficulties. At present, rather than working together, medicine and the law approach the problems differently and sometimes even thwart one another. If medicine is to take the lead, as Judge Goldberg hints it should, it will be necessary to lessen some of the restrictions which now so effectively prevent medicine from policing itself, and then it will be necessary for the medical profession to attack incompetence with the same vigor it now seeks to assure excellence. Nork (Gonzales) has lessons for all.

—MSMW

Clinical Manifestations of Hypercalcemic Disorders—A Correction

In the editorial "The Genesis of the Clinical Manifestations of Hypercalcemic Disorders," which appeared on page 333 of the October issue, an error was made in the typescript substituting the word calcium for bicarbonate. The first sentence of the fourth paragraph should read, "Second, it has been shown that non PTH-induced hypercalcemia may be associated with metabolic alkalosis, most probably due to enhanced renal tubular transport of bicarbonate."

CASE REPORTS

Refer to: Kressel HY, Gamsu G, Kalifa LG, et al: Prolonged growth arrest of pulmonary metastases in papillary thyroid carcinoma. West J Med 129:424-429, Nov 1978

Prolonged Growth Arrest of Pulmonary Metastases in Papillary Thyroid Carcinoma

HERBERT Y. KRESSEL, MD
GORDON GAMSU, MD
L. GABRIEL KALIFA, MD
W. RICHARD WEBB, MD
San Francisco

THE GROWTH RATE of pulmonary nodules is often used to help differentiate benign from malignant disease; pulmonary nodules that show no growth for more than two years are generally considered benign. However, nodular lung metastases from papillary thyroid carcinoma are an exception and may demonstrate no change in size on x-ray films of the chest obtained over many years. This phenomenon has been referred to on a number of occasions and cannot be considered rare.[1-5]

In a review of 235 consecutive inpatients with thyroid carcinoma seen at the University of California San Francisco from 1965 through 1974, 19 were found to have pulmonary metastases, and 14 of these had papillary tumors. Four patients with papillary carcinoma experienced prolonged growth arrest of metastatic nodules; x-ray films of the chest were unchanged for periods ranging from 14 to 25 years. We are reporting the cases of these four patients to emphasize the relationship of prognosis to cell type and age; the association between an increase in radiographic size of the pulmonary metastases and anaplastic shift; and the relationship between dyspnea, polycythemia and pulmonary arteriovenous shunting through metastases.

From the Department of Radiology, University of California School of Medicine, San Francisco, California.

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Submitted, revised, January 20, 1978.

Reprint requests to: Gordon Gamsu, MD, Department of Radiology, 396-M, University of California, San Francisco, CA 94143.

Reports of Cases

CASE 1. A 46-year-old woman underwent resection of a right thyroid nodule in 1943. A diagnosis of papillary thyroid carcinoma was made. Six years later a right thyroid lobectomy was performed for a local recurrence. In 1957, 14 years following the initial diagnosis, a routine x-ray film of the chest demonstrated new findings consisting of subglottic tracheal narrowing due to local tumor extension and several pulmonary nodules, 0.5 to 1.0 cm in diameter (Figure 1, A and B). There was no pulmonary uptake of iodine 131 (^{131}I). Treatment was 50 millicuries of ^{131}I and local tracheal irradiation. An x-ray film of the chest following therapy showed no change and remained unchanged for 15 years. In 1975, the patient was admitted for evaluation of hemoptysis and dyspnea. X-ray films showed enlargement of the pulmonary nodules (Figure 1, C and D). Increased encroachment on the tracheal lumen was also observed. A tracheostomy was performed, resulting in symptomatic improvement. A biopsy specimen of the tracheal lesion showed anaplastic carcinoma, for which the patient received local irradiation and chemotherapy.

CASE 2. In 1940, at the age of 12, this woman had received local irradiation for an undiagnosed neck mass (in retrospect, possibly the primary thyroid carcinoma). Twelve years later, a biopsy specimen of an enlarged cervical lymph node was interpreted as "benign aberrant thyroid tissue." In 1961, the patient, then 33 years old, was seen at our institution for evaluation of recurrence of the neck mass. An x-ray film of the chest then demonstrated several lung nodules, approximately 0.5 cm in diameter. Because of this finding, slides from the cervical node biopsy performed in 1952 were examined and, this time, interpreted as papillary thyroid carcinoma. In 1962, the patient underwent bilateral, subtotal thyroidectomy and bilateral cervical lymph node dissection; papillary carcinoma was confirmed. She has remained asymptomatic while receiving thyroid extract to suppress the tumor. X-ray films of the chest ob-

tained in 1975 (Figure 2) showed no change in the size or number of the pulmonary nodules.

CASE 3. A 12-year-old boy was seen at our institution in 1953 following the diagnosis of thyroid carcinoma with metastasis to the cervical lymph nodes. The x-ray film of the chest showed innumerable nodules 2 to 3 mm in diameter (Figure 3, A and B). The boy underwent total thyroidectomy with bilateral cervical node dissection; histologic examination of the operative specimen disclosed papillary adenocarcinoma. Pulmonary uptake of ^{131}I indicative of functioning thyroid tissue was noted. Later that year, the tumor recurred locally and was surgically removed; the patient was then treated with ^{131}I. Following this therapy, the x-ray film of the chest showed decrease in the number of nodules, but many persisted. These nodules have remained unchanged in size and number over the ensuing 20 years. The patient is presently asymptomatic and shows no pulmonary uptake of ^{131}I.

CASE 4. In 1940, a 15-year-old boy received head and neck irradiation for acne. In 1947, a partial thyroidectomy disclosed carcinoma. The patient was first seen at our institution in 1949, at the age of 24, for evaluation of a recurrent neck mass and dyspnea on exertion. An x-ray film of the chest demonstrated miliary nodules, 2 to

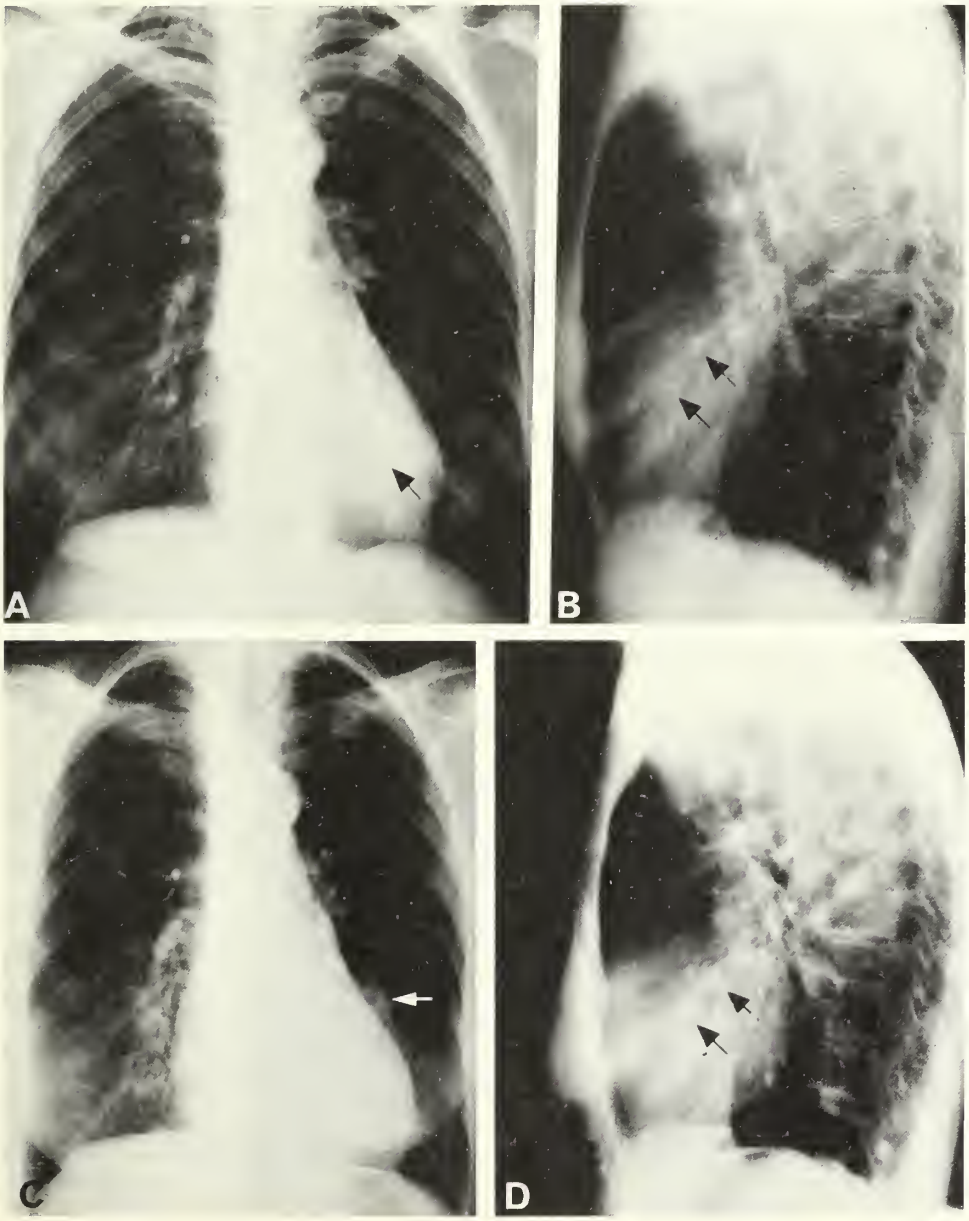

Figure 1.—Case 1. **A,** Anteroposterior, and **B,** lateral x-ray films in 1957 show several discrete pulmonary nodules **(arrows). C** and **D,** X-ray films of the chest obtained in 1975 reveal that several nodules have increased in size **(arrows).** A biopsy specimen showed anaplastic shift.

3 mm in diameter, throughout both lungs. A total thyroidectomy with left, radical, neck dissection was performed because of local recurrence. Histologic examination showed papillary adenocarcinoma.

In 1954, five years following total thyroidectomy, polycythemia was noted. Hemoglobin was 17.5 mg per dl and total red blood cell volume was twice normal (205 percent). Cardiac catheterization revealed pulmonary arteriovenous shunting. Pulmonary uptake of ^{131}I was present and open-lung biopsy, in 1957, showed metastatic papillary thyroid carcinoma. The patient was treated with 310 millicuries of ^{131}I, and pulmonary uptake of radioactive iodine diminished. No change was noted in the radiographic appearance of pulmonary nodules, and x-ray films obtained over the next 17 years showed no progression of the metastasis. During this period, the patient received dessicated thyroid for tumor suppression.

Figure 2.—Case 2. X-ray film of the chest in 1975 shows several small nodules **(arrows)** that had shown no increase in size since 1961.

In 1974, 25 years after the initial diagnosis of pulmonary metastasis, the patient noted increased dyspnea. X-ray films of the chest showed that the size and number of lung nodules had increased since 1969 (Figure 4, A, B, C). In addition, a mediastinal mass was noted. No pulmonary uptake of ^{131}I could be demonstrated. Vital capacity was 50 percent of normal.

Over the next year, obstruction of the superior vena cava developed with further progression of metastasis. Liver and brain scan findings were consistent with multiple metastases. A diagnosis of late anaplastic shift was made, and chemotherapy and irradiation to the brain and mediastinum were begun. The patient died in January 1976.

Discussion

Thyroid carcinoma is classified histologically as papillary, follicular, medullary or anaplastic; and survival following treatment correlates closely with cell type.[6-10] Papillary carcinoma bears the best prognosis and 82 percent of patients with this tumor live for ten years after diagnosis.[10] Even in the presence of metastatic spread, survival periods of patients with papillary carcinoma may exceed 20 years;[2-4,10] in these patients metastases grow very slowly or undergo long periods of growth arrest.[2-4]

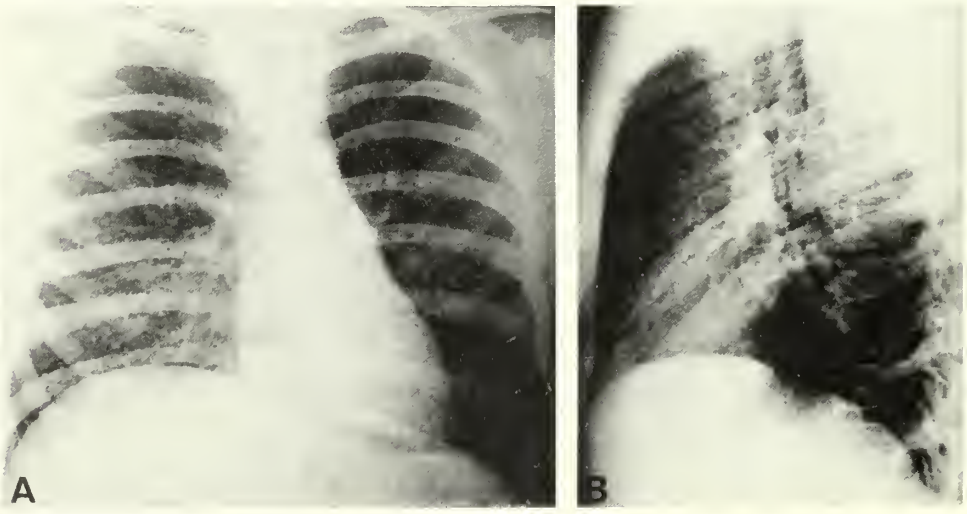

Figure 3.—Case 3. Miliary nodules are shown on **A**, anteroposterior, and on **B**, lateral x-ray films obtained in 1953.

We are reporting the cases of four patients with papillary thyroid carcinoma and prolonged growth arrest of pulmonary metastases; only five such cases have been previously described in the same detail (Table 1).[1-5] For this report, we have used the histologic classification of Woolner and coworkers[10] and of Franssila,[7] which regards as papillary any tumor with papillary elements including those with mixed papillary and follicular elements. In our four patients, pulmonary nodules were unchanged in size, number and appearance for periods ranging from 14 to 25 years. To our knowledge, growth arrest of similar duration does not occur in patients with follicular, medullary or anaplastic thyroid carcinomas.

The cause of arrest of metastatic growth in papillary thyroid carcinoma is unknown. Although each of our patients received ^{131}I treatment or thyroid hormone for tumor suppression, growth arrest has occurred without irradiation or chemotherapy.[1-4] In some cases,[2,3] endogenous thyroid hormone may be sufficient to suppress tumor growth; immunologic and nutritional factors have also been proposed as being important to the biologic control of metastatic tumor.[1,2] In untreated patients with papillary thyroid carcinoma, metastatic pulmonary nodules have been stable for periods of up to 28 years.[1-4]

In patients with papillary thyroid carcinoma, age is important in determining prognosis.[10-12] Patients less than 40 years old at the time the primary tumor is diagnosed survive longest,[10] despite the common occurrence of metastasis to local lymph nodes in this group.[8,10,12] McKenzie[8] studied 39 patients with thyroid carcinoma who were less than 40 years of age; 74 percent of them had lymph node metastases, yet none died during a follow-up period of 10 to 15 years. Not surprisingly, most patients with prolonged arrest of pulmonary metastasis also fall within this age group. The average age of the nine patients listed in Table 1 is 24 years. This is considerably less than the average age of all patients with papillary thyroid carcinoma,[10] and probably reflects a potential among young patients for biologic control of the tumor.

Irradiation to the head and neck has been implicated in 50 percent to 80 percent of all childhood thyroid carcinomas,[6,12,13] and in 15 percent of thyroid carcinomas regardless of age.[13] Papillary adenocarcinoma is the most common histologic type associated with previous irradiation. Two of our four patients had had previous cervical irradiation (although in one the irradiation may have been for the primary lesion). This information is not available in previous reports.

Pulmonary metastases were multinodular in each of our patients; two had diffuse miliary disease and two had larger, more discrete nodules. Similar patterns have been recognized by others,[1-5] and calcification of nodules due to aggregation of psammoma bodies has occurred.[3,5] In both of our patients with a miliary pattern of metastasis, pulmonary uptake of ^{131}I occurred. In each, uptake diminished following radioiodine therapy. Radiologic recognition of pulmonary nodules has preceded the diagnosis of papillary thyroid carcinoma by more than 22 years,[3] but in most patients pulmonary metastases are detected at the time of or within two years following the initial diagnosis (Table 1). Delayed metastatic spread to the lungs has occurred but is not common. Anaplastic shift (a change in tumor type from papillary to anaplastic carcinoma) can occur years after the initial diagnosis.[14-16] Although in most cases the shift follows irradiation, it may

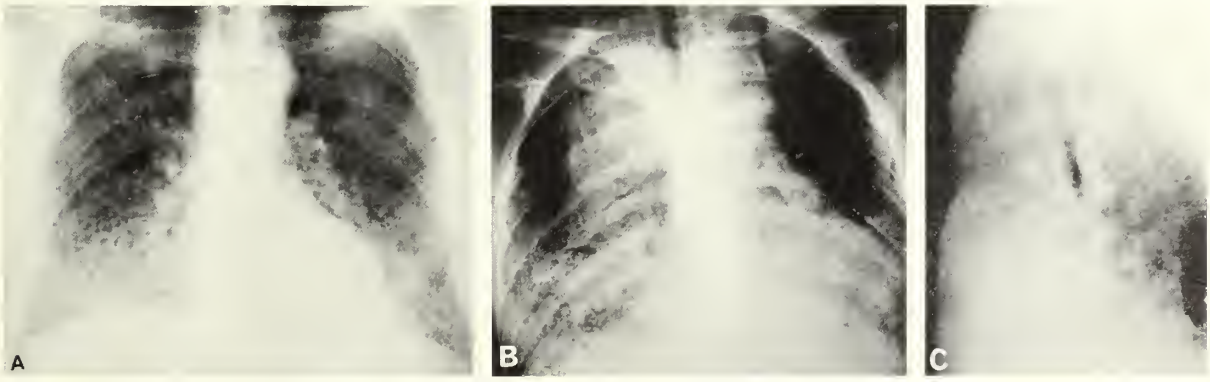

Figure 4.—Case 4. **A,** x-ray film of the chest in 1969 shows miliary metastasis that had not changed since 1954. **B,** Anteroposterior, and **C,** lateral views in 1975 show confluent miliary metastasis and a large mediastinal mass.

TABLE 1.—*Prolonged Growth Arrest of Pulmonary Metastases in Thyroid Carcinoma*

	Age,Sex	*Previous Irradiation*	*Primary Tumor*	*Node Metastases*	*Therapy*	*Diagnosis to Discovery of Pulmonary Metastases (Years)*	*Symptoms*	*Roentgenographic Features*	*Pulmonary ^{131}I Uptake*		*Duration of Growth Arrest (Years)*	*Other*
									Before Therapy	*After Therapy*		
Everson and Cole[1] ..	6,F	..	Papillary	Yes	Irradiation	7	None	Diffuse nodules	..	..	16	..
Irving and Payne[2] ..	39,F	..	Papillary	Yes	Subtotal thyroidectomy, irradiation	0	None	Three nodules	Yes	..	28	..
Knowles[3]	33,F	..	Papillary	No	..	Pulmonary metastases preceded diagnosis of primary by 22 years	None	Multiple nodules, calcification	No	..	22	..
McGee and Warren[4] .	19,F	..	Papillary	..	Subtotal thyroidectomy	2	Dyspnea	Diffuse nodules	..	..	24	Arteriovenous shunting, polycythemia
Pierce and co-workers[5]	17,M	..	Papillary	Yes	Irradiation	0	Dyspnea	Disffuse miliary nodules, calcification	..	Yes	14	Arteriovenous shunting, polycythemia
Kressel and co-workers												
Case 1	46,F	No	Papillary	Yes	Subtotal thyroidectomy, ^{131}I, irradiation	14	None	Multiple nodules (0.5 to 1.0 cm)	No	..	18	Anaplastic shift
Case 2	24,F	Yes	Papillary	Yes	Subtotal thyroidectomy, ^{131}I, irradiation	9	None	Multiple nodules (0.5 cm)	No	..	14	..
Case 3	12,M	No	Papillary	Yes	Total thyroidectomy, ^{131}I, thyroid suppression	0	None	Miliary nodules	Yes	No	20	..
Case 4	22,M	Yes	Papillary	Yes	Total thyroidectomy, ^{131}I, irradiation	2	Dyspnea	Diffuse miliary nodules	Yes	No	25	Arteriovenous shunting, polycythemia, anaplastic shift

occur without irradiation.[9,15] Anaplastic shift bears a grim prognosis, and the majority of patients die within one year of its detection.[14-16] In two of our patients, a change in the size of metastatic nodules that had been stable for 15 to 17 years heralded an anaplastic shift—an occurrence that has not been previously reported. Although such growths can occur without a change in the histologic appearance of the tumor, we believe that rapid enlargement of pulmonary lesions in a patient with previously stable metastasis suggests the presence of anaplastic shift and indicates the need for biopsy.

Respiratory symptoms are uncommon in patients with thyroid carcinoma that metastasizes to the lungs. Only one patient in our group was symptomatic at the time pulmonary metastases were detected; dyspnea on extertion was his only complaint. During his illness this patient developed polycythemia that was due to hypoxemia resulting from pulmonary arteriovenous shunting within highly vascular metastases. This arteriovenous shunting is known to occur in patients with metastatic thyroid carcinoma,[5] and an identical case, with angiographic confirmation, was reported by McGee and Warren.[4] In such patients, innumerable nodular densities appear on x-ray films of the chest. Probably, diffuse pulmonary metastases are necessary to produce shunting of such a magnitude that arterial oxygen desaturation and polycythemia will result.

Summary

This report presents four cases with the uncommon finding of unchanging pulmonary nodules due to metastatic papillary thyroid carcinoma. Radiographic follow-up periods ranged from 14 to 25 years. Three patients were less than 40 years of age at the time of first diagnosis; this reflects the good prognosis for young people with this disease. Three patients were initially asymptomatic, but the fourth had dyspnea that probably resulted from pulmonary arteriovenous shunting associated with miliary metastases. Rapid growth of previously stable metastatic nodules in two patients suggests anaplastic shift, and this finding may indicate the need for lung biopsy.

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Disposition of Acetone Following Acute Acetone Intoxication

AVNER RAMU, MD
JAMES ROSENBAUM, MD
TERRENCE F. BLASCHKE, MD
Stanford, California

ALTHOUGH ACETONE is a component of a large variety of industrial and household cleaners, glues and solvents, acute acetone intoxication has not been frequently reported.[1,2] Acetone is relatively nontoxic; ingestion of as much as 200 to 400 ml may not result in serious sequelae.[3,4] Symptoms of mild acetone intoxication are characterized by drowsiness and incoherent speech,[1,2] while in more severe cases stupor and deep coma may result. Since acetone is excreted by the lungs, the odor of acetone is always found on the patient's breath. The effects of acetone are said to be similar to those of ethanol at equal blood levels, although the anesthetic potency is greater.[5] There is little information about the kinetics of the disappearance of acetone in persons following

From the Department of Medicine, Division of Clinical Pharmacology, Stanford University School of Medicine.

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Reprint requests to: Terrence F. Blaschke, MD, Division of Clinical Pharmacology, Room S-155, Stanford University Medical Center, Stanford, CA 94305.

acute oral ingestion.[4,5] In this report we describe the clinical symptoms and the kinetics of elimination of acetone in a patient who presented on two occasions with acute acetone intoxication.

Report of a Case

A 53-year-old woman was brought to the emergency room after her sister found her in a lethargic, minimally responsive state. During the previous week, neighbors had noted that she seemed increasingly lethargic and unsteady. She had had multiple previous medical and psychiatric admission for acute and chronic alcohol abuse. Pertinent medical history included biopsy-proven Laennec cirrhosis and a history of a portacaval shunt done 13 years earlier for upper gastrointestinal bleeding presumed to be secondary to varices. Other complications of alcoholism included a peripheral neuropathy and cerebellar atrophy as well as alcoholic withdrawal seizures. Two years before this admission she had suffered a cerebrovascular occlusion resulting in temporary aphasia and a residual right-sided weakness, and she required a cane for ambulation. Her medications at the time of admission were phenytoin and phenobarbital for seizure control and furosemide and potassium chloride for mild hypertension. At the time of physical examination she appeared as a tremulous female who had a fruity odor on her breath and a tendency to pick frequently at her hair. Her vital signs were normal. The oral mucosa showed no ulceration or injection. Results of chest and cardiac examination were unremarkable. Abdominal examination revealed a liver with a span of approximately 10 cm. Other findings of the general physical examination were essentially within normal limits. Neurological examination showed that the patient was oriented, lethargic but arousable, and had a shortened attention span. She was able to follow simple commands. Cranial nerves were intact and reflexes were symmetric with no pathological reflexes. Gait was broad-based but otherwise motor and sensory examination showed no gross abnormalities. Analysis of urine revealed a specific gravity of 1.017 and a 3+ value for ketones but no glucose. Arterial blood gas studies showed a pH of 7.51, arterial oxygen pressure (Pa_{O_2}) of 81 mm of mercury and arterial carbon dioxide pressure (Pa_{CO_2}) of 27 mm of mercury. Toxicology screening of blood showed a phenytoin level of less than 2.5 μg per ml, a phenobarbital level of 15 μg per ml, and an acetone concentration of 0.25 gram per dl, measured by gas chromatography. The blood ethanol and isopropanol levels were zero. Acetone was detectable in material obtained from a gastric aspiration. The patient was admitted for observation, and over the next 72 hours she demonstrated slowly progressive improvement in her level of consciousness. Subsequently, a half-empty bottle of nail-polish remover was found in the patient's home but she denied ingesting its contents.

Approximately a month later, the patient was again brought to the emergency room with a one-day history of increasing lethargy and somnolence. Results of physical and laboratory examinations were similar to those from the previous admission. Toxicology examination again revealed a blood acetone concentration of 0.25 gram per dl. The patient was admitted for observation and showed gradual improvement in her mental status as acetone levels declined (see Figure 1). After five days she was transferred to an alcoholic rehabilitation center for long-term control and management of her alcohol problem.

Discussion

A definite history of acetone ingestion could not be obtained from this patient on either of her two admissions. Detectable concentrations of acetone in the blood may be observed in several other clinical settings. In diabetic ketoacidosis, for example, the range of acetone concentrations found is approximately 0.01 to 0.07 gram per dl.[4,6] In isopropyl alcohol intoxication, acetone concentrations in plasma and breath may be measured due to the metabolic conversion of isopropyl alcohol to acetone. However, the high concentration of acetone observed in this patient could have resulted only from the direct ingestion of acetone. Two reported signs of acute acetone ingestion are a red and swollen pharynx and erosions of the soft palate. These were not seen in this patient, and it is likely that the acetone was diluted in another liquid and taken over a period of time. This reconstruction is supported by the gradual development of symptoms on both occasions over a period of several days.

Surprisingly few data are available regarding the human rate of elimination of acetone, particularly at the high blood levels seen in intoxicated patients. Haggard and co-workers[5] studied volunteers who drank as much as 80 mg per kg of body weight of acetone; they found that the maximal concentration of acetone in blood was

about 0.007 gram per dl. They calculated that, at this concentration, 70 percent of the total elimination of acetone was due to metabolic conversion and that the fraction of elimination due to metabolism increases as the concentration falls. These data of Haggard and those of DiVincenzo[7] indicate nonlinear and saturable metabolism of acetone at concentrations much lower than those seen in patients with acute acetone intoxication.

Saturable metabolism of acetone has also been documented in rats, with a zero-order elimination rate of 13 mg per kg of body weight per hour being reached at a concentration of 0.2 gram per dl.[5] The maximum rate of metabolism in humans is not known, but comparison of the human data[5] with the data in rats at similar concentrations suggests that the maximum metabolic rate on a weight basis would be lower in humans. For a patient of average size, metabolic conversion of acetone probably cannot exceed 1 gram per hour.

The volume of distribution of acetone (which is a measure of the fraction of drug in the body that is found in the blood) is estimated to be about

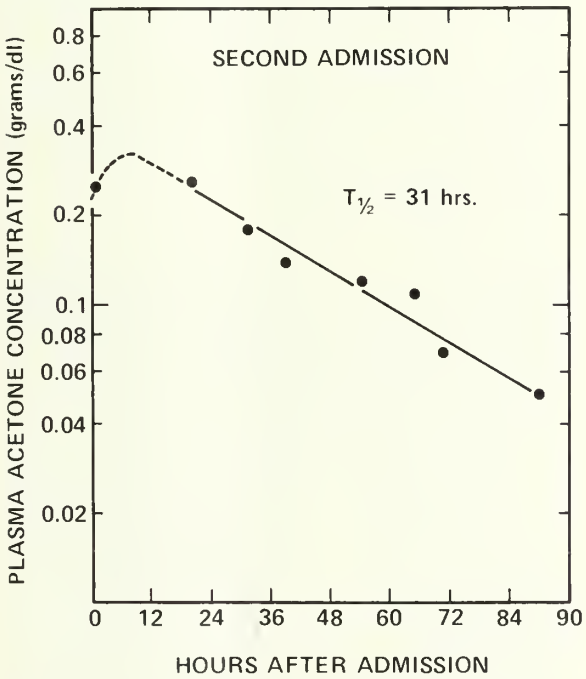

Figure 1.—Time course of acetone concentrations in blood following the second admission for acetone intoxication. The half-life, calculated by nonlinear least squares regression analysis of the data from 19 hours after admission and beyond, is 31 hours. This is similar to a half-life of 28 hours calculated on the first admission with fewer data points. Although there is considerable scatter in the data, they appear to be log-linear and consistent with a first-order elimination process.

0.82 liter per kg or 82 percent of body weight, which is approximately equal to total body water.[5] Based on a concentration of acetone of 0.25 gram per dl at the time of admission, it can be estimated this patient had about 150 grams of acetone in her body. Allowing for some possible continued absorption during the first several hours after admission, the disappearance of acetone from blood appears to follow a log-linear (or first-order) pattern, with a half-life of 31 hours, as calculated by the nonlinear regression program MLAB (Modeling Laboratory).[8] During the 19-hour interval between the collection of the second and fourth acetone samples, roughly 75 grams of acetone were eliminated from her body, well in excess of the 19 grams that could be due to metabolic conversion of acetone. Urinary excretion of acetone is minimal; the patient's urine/blood concentration ratio for acetone was found to be 1.08, similar in magnitude to that reported by others.[5,9]

The remaining, and most important, route of elimination of acetone in the acutely intoxicated patient is therefore the respiratory tract. Haggard and co-workers[5] and Briggs and Schaffer[9] have found that the concentration ratio of acetone in blood/alveolar air is 330. This means that 330 liters of alveolar air must be exchanged to "clear" the acetone from 1 liter of blood. Using an average minute ventilation of 9.65 liters per minute based on this patient's age, weight and sex,[10] the clearance of acetone by the lungs can be calculated to be 29 ml per minute, or 0.39 ml per minute per kg of body weight. With a volume of distribution of 0.82 liter per kg of body weight, the half-life would be expected to be 25 hours. This figure is in reasonable agreement with the half-life observed in this patient. The extent to which this patient's liver disease contributed to the long half-life cannot be assessed, but it is probably minor, considering the low concentrations at which metabolism is saturated in subjects with normal liver function.

It is apparent from the above discussion that at concentration above 0.1 gram per dl, the rate of elimination of acetone is determined by the respiratory execretion rate. The pulmonary clearance, however, is low; and thus the half-life of acetone is relatively long, more than 30 hours in this patient. Theoretically, one might increase the pulmonary clearance by means of hyperventilation, but the toxicity of acetone is so low that

this approach would probably not be frequently justified. As with this patient, improvement is gradual and follows a time course similar to the decline seen in blood acetone concentrations. Clinically, it is important to recognize that the time required for recovery of these patients is measured in days, and that acetone concentrations may be useful in distinguishing acetone intoxication from other causes of central nervous system depression.

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Pancreatitis as the Presenting Manifestation of Miliary Tuberculosis

JAMES L. RUSHING, MD
San Jose, California

CAROL J. HANNA, MD
PAUL A. SELECKY, MD
Torrance, California

THE CLINICAL PRESENTATION of miliary tuberculosis may take many forms. Some of these are quite nonspecific and obscure,[1-3] making the diagnosis very difficult at times. Although not widely appreciated, it is not uncommon for abdominal pain to be a major clinical finding. This has been attributed largely to tuberculous infiltration of the peritoneum and gastrointestinal tract.[2,4] Pancreatitis and hyperamylasemia, however, are exceedingly rare features of miliary tuberculosis[5,6] and neither has been previously reported as a presenting feature of this disease.

The association of the adult respiratory distress syndrome (ARDS) and miliary tuberculosis is also an uncommon occurrence. Only six cases have been reported.[7-10] We recently cared for a patient in whom both pancreatitis and a transient episode of ARDS developed as complications of miliary tuberculosis. Because each of these conditions is a distinctly unusual feature of disseminated tuberculosis infections, we wish to report our experience.

Report of a Case

The patient was a 39-year-old black man admitted with a three-week history of intermittent right upper quadrant abdominal pain and a one-week history of fever, malaise, nausea and vomiting.

The patient said that he did not use alcohol, did not smoke and had not been exposed to tuberculosis. He was told he had sarcoidosis at another hospital seven years previously—the diagnosis based on abnormal findings on a roentgenogram of the chest. No further studies were carried out, and he was not treated. His past history was otherwise noncontributory.

On physical examination at admission the patient was noted to be well-developed and thin; body temperature was 39.4°C (103°F). Mild epigastric tenderness was elicited by palpation; neither organomegaly nor rebound tenderness was present. The other findings from the examination were noncontributory.

A roentgenogram of the chest done at admission (Figure 1) showed bilateral hilar and right paratracheal lymph node enlargement. An electrocardiogram showed no abnormalities. A complete blood count gave the following values: hemoglobin, 14.2 grams per dl; hematocrit, 41.4 percent; leukocyte count, 4,800, with 19 percent bands, 52 percent polymorphonuclear cells, 17 percent lymphocytes and 12 percent monocytes. Analysis of urine showed 1+ protein by dipstick and up to two leukocytes per high-power field; other results were within normal limits. Electrolytes and blood urea nitrogen were normal, as were the prothrombin and partial thromboplastin times. The serum glutamic-oxaloacetic transami-

From the Departments of Medicine (Drs. Rushing and Selecky), and Pathology (Dr. Hanna), UCLA School of Medicine and Harbor General Hospital, Torrance. Dr. Rushing is now with Stanford University School of Medicine and Santa Clara Valley Medical Center, San Jose.

Submitted September 28, 1977.

Reprint requests to: James L. Rushing, MD, Respiratory Medicine, Santa Clara Valley Medical Center, 751 South Bascom Avenue, San Jose, CA 95128.

nase (SGOT), alkaline phosphatase and total bilirubin levels were abnormal (SGOT, 520 mIU per ml [normal, 10 to 30 mIU per ml], alkaline phosphatase, 247 mIU per ml [normal, 36 to 92 mIU per ml], total bilirubin, 1.4 mg per dl [normal, 0.1 to 1.2 mg per dl]). The serum amylase value was 332 Somogyi units per dl (normal, 30 to 194 Somogyi units per dl). Skin tests showed no reaction to coccidioidin 1:10 or purified protein derivative intermediate (5 TU) and second strength (250 TU). There was 15 mm induration to mumps antigen.

The patient was treated conservatively: fluid was administered intravenously and oral intake was stopped. Temperature spikes to 40°C (104° F) continued to occur. Bacterial cultures of blood, urine and sputum were repeatedly negative. On the ninth hospital day, the patient became dyspneic and tachypneic. Arterial blood gas studies on room air showed an arterial oxygen pressure (Pa_{O_2}) of 25 mm of mercury, an arterial carbon dioxide pressure (Pa_{CO_2}), 25 mm of mercury and a pH of 7.48. A roentgenogram of the chest (Figure 2) showed alveolar infiltrates with no cardiomegaly. On physical examination there was tachycardia without S3 or S4. The lungs were clear to auscultation and there was no peripheral edema or signs of volume depletion. Maximum nasal and mask oxygen supplementation failed to provide adequate oxygenation. An orotracheal tube was inserted, and the patient was placed on a volume ventilator, requiring fraction of inspired oxygen (FIO_2) of 1.0 for adequate oxygenation. Fiberoptic bronchoscopy was carried out and bronchial brushings were collected. Stains for routine bacteria, acid-fast, fungal and Pneumocystis organisms were negative on these specimens.

The patient was begun on a regimen of methylprednisolone, 100 mg given intravenously every six hours, for treatment of the ARDS. Oral administration of isoniazid (300 mg per day) and ethambutol (25 mg per kg of body weight per day) was started but was discontinued after five days because of worsening liver function and the lack of documented tuberculosis. The steroids were tapered and discontinued over the course of one week. The arterial blood gas values and findings on a roentgenogram of the chest improved on the above regimen, and the patient was successfully extubated six days later (15th hospital day). Postextubation arterial blood gases at FIO_2 of 0.3 were an arterial oxygen pressure of 66 mm of mercury, an arterial carbon dioxide pressure of 30 mm of mercury and a pH of 7.45.

Despite this response, the patient continued a deteriorating course with persistent temperatures to 39.4°C (103°F), intermittent lethargy, nausea, vomiting and abdominal pain. Extensive laboratory studies failed to reveal a cause other than pancreatitis and hepatitis. The SGOT value reached a peak of 900 mIU per ml and then declined to 150 mIU per ml. Similarly, the serum bilirubin reached a peak of 9.2 mg per dl and declined to 2.6 mg per dl. The serum amylase was consis-

Figure 1.—Admission roentgenogram of the chest showing bilateral hilar and right paratracheal lymph node enlargement with clear lung fields.

Figure 2.—Supine roentgenogram of the chest showing bilateral alveolar infiltrates without cardiac enlargement.

tently elevated, reaching a maximum level of 920 Somogyi units per dl. Urinary diastase was 61,750 units per 24 hours at that time. Amylase/creatinine clearance ratios were determined serially throughout the patient's course and were consistently greater than 6:1.

The patient became progressively weak and lethargic, and urine output decreased. On the 28th hospital day a cardiac arrest occurred and there was no response to resuscitation efforts.

After the patient's demise, the antemortem bronchial brushing cultures were reported as positive for Mycobacterium tuberculosis.

Findings at Autopsy

At autopsy the lungs were heavy and diffusely firm, and had multiple areas of consolidation. The right lung weighed 1,400 grams (normal 450 grams); the left lung weighed 890 grams (normal 375 grams). Numerous small subpleural and peribronchial soft yellow-white nodules, averaging 1 mm or less in diameter, were evident. Viewed microscopically, there were small foci of acute necrosis which contained scattered polymorphonuclear leukocytes and occasional lymphocytes. The alveolar walls were edematous and were the site of a mixed acute and chronic cellular infiltrate. Numerous lipid-laden macrophages and large collections of hyaline membranes lined the air spaces, which also contained focal fresh blood (Figure 3A and 3B). In addition, there were collections of intraalveolar and intrabronchial polymorphonuclear leukocytes and fibrin.

The *hilar lymph nodes* were notably enlarged, varying in consistency from areas which were softly fluctuant to areas of rubbery fibrosis. The cut sections displayed caseous material. On microscopic examination these nodes showed multiple hyalinized granulomata indicating focal areas of peripheral breakdown with associated moderate mononuclear cell infiltration.

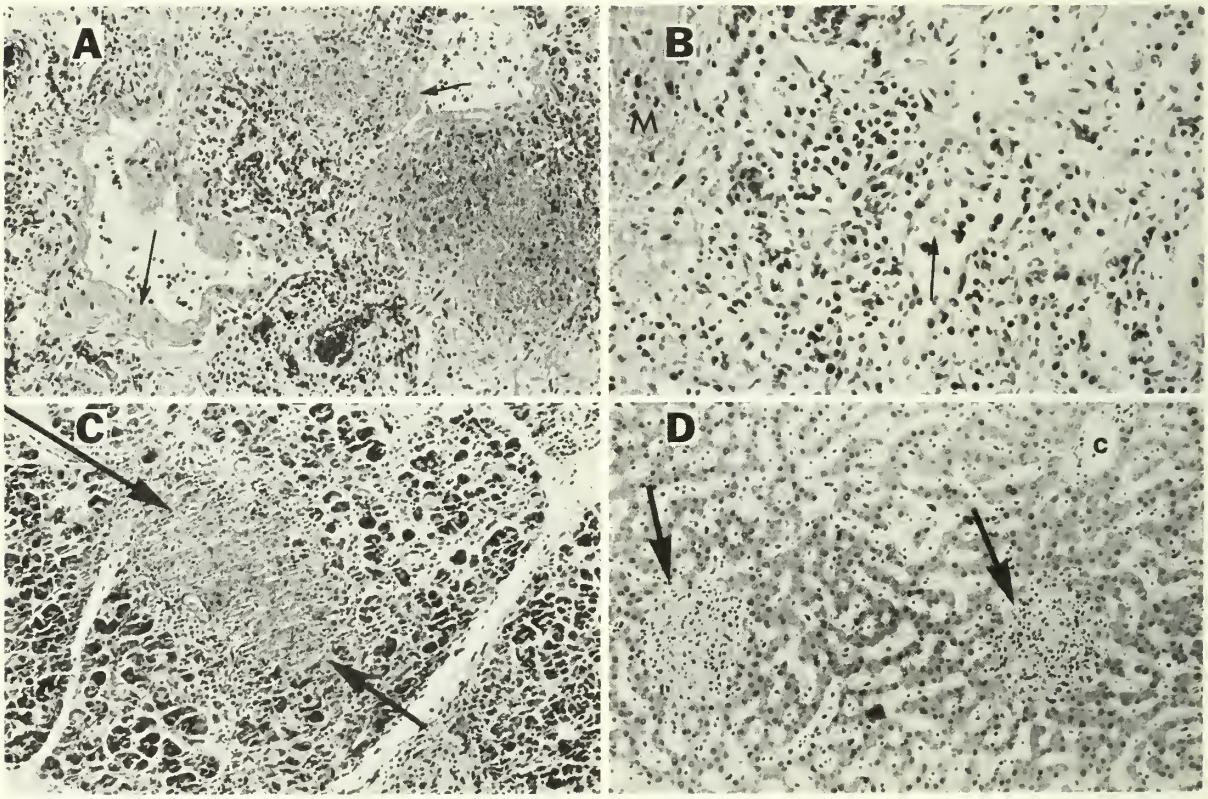

Figure 3.—Photomicrographs from hematoxylin and eosin stained sections obtained at autopsy, **A.** Pulmonary parenchyma with acute tuberculous microabscesses and extensive hyaline membrane formation **(arrows). B,** Pulmonary parenchyma with alveolar septal edema, intraalveolar pulmonary macrophages **(arrow),** and a mixed acute and chronic inflammatory cell infiltrate. M = microabscess. **C,** Pancreatic acinar tissue showing an acute tuberculous microabscess **(arrows). D,** Liver with multiple acute tuberculous microabscesses **(arrows).** Note the hepatic cords and sinusoids retain normal architecture. C = central vein. (Enlarged from original magnification ×110.)

Although the *pancreas* was unremarkable grossly, multiple small acute microabscesses, similar to those described in the lung, were microscopically observed affecting the acinar tissue but not the islets (Figure 3C). The liver (Figure 3D), cerebrum, retinas, heart, kidneys and prostate all had similar microabscesses. Notably, small clusters of acid-fast bacilli were found in all acute microabscesses.

Comments

Abdominal pain has been described as a major symptom in 7 percent to 14 percent of patients with miliary tuberculosis. This has been attributed to peritonitis, enteritis and retroperitoneal lymphadenitis,[1,2,4] but the presentation of this disease as pancreatitis has not been previously described. As many as 14 percent of patients with miliary tuberculosis have been reported to have pancreatic involvement at autopsy;[4,6] however, no mention is made of hyperamylasemia or clinical signs of pancreatitis in these reviews.

The histologic studies in our patient showed multiple microabscesses in the pancreas typical of miliary tuberculosis. Similar abscesses were present in multiple other organs, although the peritoneum, gastrointestinal tract and retroperitoneal nodes were not involved. This would indicate that the pancreas was the primary cause of abdominal pain. Other causes of pancreatitis, such as obstructed pancreatic ducts, evidence of biliary disease or a history of excessive alcohol intake, were not present.

Infectious agents have been described as being a cause of acute pancreatitis in up to 20 percent of cases.[7] The most common blood-borne organism is the mumps virus, although bacterial microabscesses have also been reported in the pancreas after septicemia. The subsequent destruction of the tissue surrounding these abscesses causes an outpouring of pancreatic enzymes into the bloodstream and surrounding tissues, resulting in the typical clinical and laboratory findings seen in our patient.

The adult respiratory distress syndrome (ARDS) is also a rare complication of miliary tuberculosis.[8] ARDS is characterized by progressive hypoxemia which is unresponsive to high concentrations of inspired oxygen, decreased lung compliance and diffuse alveolar infiltrates shown on roentgenograms of the chest.

Of the numerous factors invoked as causes of ARDS, increased capillary permeability is prominent.[9] The postulated mechanisms leading to this abnormality in miliary tuberculosis include (1) the presence of large numbers of mycobacteria in the pulmonary circulation producing damage to capillary endothelial cells; (2) platelet-fibrin microemboli in the pulmonary capillaries inducing endothelial injury; (3) a hypersensitivity reaction to the mycobacteria resulting in endothelial damage.[8]

Huseby and Hudson[8] noted that five of the six reported cases of ARDS due to tuberculosis had disseminated intravascular coagulation, suggesting to them that microembolization of fibrin-platelet aggregates played an important role in the pathogenesis of the syndrome. In our patient, however, disseminated intravascular coagulation never developed. The possibility exists that in this patient ARDS may have been a result of pancreatitis, which has been associated with increased pulmonary capillary permeability.[10] However, it is important to note in this regard that the ARDS improved while the pancreatitis remained unchanged. Likewise, cultures of bronchial brushings obtained while the patient had clinical and roentgenologic evidence of ARDS later grew M. tuberculosis. This suggests to us that the mycobacteria in the pulmonary parenchyma were important in the pathogenesis of the ARDS. The fact that the syndrome cleared with minimal antituberculosis therapy and administration of steroids in high doses favors the role of a hypersensitivity or immune reaction.

Miliary tuberculosis is generally a curable disease. The need for a high index of suspicion and early diagnosis is obvious. Our experience with this patient documents that pancreatitis and the adult respiratory distress syndrome may be manifestations of miliary tuberculosis. Their unexplained presence in an appropriate clinical setting should raise the suspicion of miliary tuberculosis and biopsy specimens of appropriate accessible organs (such as liver, bone marrow and lung) should be obtained.[11]

Summary

A patient who presented with pancreatitis was found at postmortem examination to have unsuspected acute miliary tuberculosis with extensive involvement of the lungs and the pancreas. Also the adult respiratory distress syndrome de-

veloped transiently during the course of disease. Either entity may be a manifestation of miliary tuberculosis; their unexplained occurrence should raise suspicion of this disease.

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Advantages of Transplantation Over Dialysis for End-Stage Kidney Disease

A PATIENT ON HEMODIALYSIS is not by any means a well patient. And there are advantages to transplantation. The patient on chronic dialysis generally runs a hematocrit of 17 percent to 20 percent, and he looks and acts and feels like he has a hematocrit of 17 percent to 20 percent. He has an extraordinarily restricted diet. The transplant patient's hematocrit improves, and his diet is almost completely liberalized in most instances. The transplant patient is not tied to that dialysis machine and the rigid three-times-a-week schedule either in a unit or in his home. Every dialysis patient has secondary hyperparathyroidism. His vitamin D metabolism is off, his calcium metabolism suffers, and they all have thinned bones and can get into serious complications. That disease is generally reversed with transplantation. There is an overall improvement in the general condition. Children who suffer renal failure and go onto dialysis do not grow; they do not enter puberty, and it is extremely gratifying to see a child grow and reach puberty after a successful transplantation. There is tremendous financial advantage to all of us, because we all pay for this program, and it is much more economical to use transplantation in a patient than to carry out chronic dialysis.

—CHARLES T. FITTS, MD, *Charleston, South Carolina*

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Facts on Ballistics

To the Editor: I have just completed reading in the August issue the Trauma Rounds article discussed by Dr. James M. Wilson, "Shotgun Ballistics and Shotgun Injuries." There are several unfortunate errors in the article concerning the technical information provided on shotgun loadings. Among the more obvious is the comment that shotgun powders are dangerous when used in handgun cartridge loadings. Many shotgun powders are very useful for handgun loads. Additionally, the weights of shotgun and pistol projectiles mentioned in the article are inaccurate as stated in grams; I believe the author meant grains. A .357 magnum revolver usually fires a 125 to 158 grain projectile rather than one weighing 90 grams. Certainly a shotgun firing a 295 gram projectile would be fearsome as this is almost three quarters of a pound of lead.

SPENCER L. KULICK, MD
San Luis Obispo, California

* * *

To the Editor: The article by Wilson on shotgun wounds was most informative, but it contained a few minor errors. Kinetic energy of a moving object is, of course, given by $\frac{1}{2}$ MV^2; there is no "g" in the formula. Dr. Wilson correctly states that the diameter of a pellet of 00 buckshot is $\frac{1}{3}$ inch, but then goes on to translate this to .22 caliber, rather than the correct .33 caliber. The correct weight of a 12-gauge slug is $\frac{7}{8}$ ounce or about 25 grams (not 295 grams) and that of a .357 magnum (or .38 special) bullet is 158 grains or about 10.2 grams (not 90 grams). The standard load of buckshot contains 9 of these .33 caliber pellets, as noted, but police and others frequently use magnum loads containing 12 or (in 3-inch magnum) 15 such pellets. Of additional interest is the fact that either a 12-gauge slug or 00 buckshot can penetrate at least two plaster-and-wood walls, or a car door, further emphasizing the lethal nature of this weapon and the danger of using it inside buildings or in heavily populated areas.

JOHN J. MORGAN, MD
Los Angeles

Dr. Wilson Responds

To the Editor: I wish to thank Drs. Kulick and Morgan for their comments concerning the article on shotgun injuries. They have both pointed out a confusing typographical error in that, as they have noted, the word *grams* should read *grains*.

Dr. Kulick's comment that shotgun powders are used in handgun loadings is true; however, the statement made in the text was in regard to the use by novices in home loading. For example, if, by mistake, equivalent weights of shotgun powders are used in pistol cartridges, excessive pressures will be generated. Thus, a great deal of care must be exercised in using these faster burning powders in pistol or rifle cartridges. Also, Dr. Kulick's correction of 90 grams to 90 grains is correct. However, the range weights of projectiles for a .357 magnum is incorrect. Indeed, a 90-grain bullet for the .357 magnum is commercially available (Smith and Wesson).

Dr. Morgan states that there is no "g" in the kinetic energy equation; indeed, the acceleration of gravity "g" appears in this and several other equations dealing with higher order ballistics. If one wishes to express the kinetic energy in footpounds (which is the unit used in all standard ballistics tables), the result ($\frac{1}{2}$ MV^2) in poundals must be divided by the acceleration of gravity (32.2) to obtain footpounds. This conversion is amply explained by DeMuth (*Journal of Trauma* 9:27-38, 1969) and can be found in any standard textbook on ballistics.

The comparison of buckshot to the .22 bullet by approximate overall size is correct. The article does not translate this to mean caliber. If one considers the fact that the weights and velocities (at certain ranges) are approximately the same for buckshot and the .22 bullet, then the kinetic energy on impact is approximately the same—which, after all, is the most important factor with respect to wounding potential (DeMuth, *Journal of Trauma* 11:219-229, 1971). A comparison based solely on caliber would not be appropriate, since a .33 caliber bullet and buckshot would

probably have different kinetic energy values, depending upon their respective weights.

Again, I wish to thank Drs. Kulick and Morgan for their comments and interest.

JAMES M. WILSON, MD
San Francisco

Sex Education for Teenagers

To THE EDITOR: This wonderful, health conscious nation of ours is suffering from a serious social sickness that is fast approaching epidemic proportions. Last year there were over a million cases of this malady, and in almost half of them there was surgical intervention. The price to the taxpayer amounted to hundreds of thousands of dollars, and those afflicted faced a heavy burden of physical pain, mental anguish and possible lifelong disability. And, sadly, this ailment strikes our female population between the ages of 15 and 19, in the early bloom of youth. This neglected health problem is, of course, teenage pregnancy.

The cold, disturbing facts are there. We in the medical profession are confronted with these statistics: There were more than a million teenage pregnancies in this country last year, and this figure continues to grow. Four hundred thousand of these illegitimate pregnancies were terminated by abortion. One out of every ten adolescent girls is a mother before she graduates from high school. Of the pregnancies that went to term over 90 percent were kept by the child-mother in a fatherless home, most often supported by welfare at taxpayers' expense. It is conservatively estimated that every illegitimate child costs society $100,000 over a lifetime of welfare assistance.

Where do we put the blame for this national illness? And is there a cure? We physicians are at least partly responsible. Collectively we have done a poor job of educating our patients and the public. Accused of this, we point the finger at our medical schools saying they didn't prepare us for this task. California Assemblyman John Vasconcellos observed that "although physicians are the persons most commonly asked for advice about sexual problems, they are the least prepared to help in this area." Under his sponsorship the California Assembly has passed legislation directing medical schools to include at least 30 hours of human sexuality courses in their curricula.

In Idaho physicians are beginning to show signs of awareness about this subject. At the recent meeting of the House of Delegates of the Idaho Medical Association two health education resolutions were introduced: One urged the medical profession to take a positive stance in behalf of family life and sex education. The other asked the medical association to go to the governor and the legislature, requesting funds to (1) supply courses at the college level to educate the educators who will teach our school children about human sexuality and (2) set up a system of certification in order to identify those people qualified to teach health education. One speaker was roundly applauded when he said "Let's take sex education out of the hands of broken-down jocks." Uncouth, yes, but undeniably said with a ring of truth.

In the final analysis, when a decision had to be made, the IMA delegates took the easy way out by referring the resolution back to the Council, to be referred, in turn, to the "proper committee." And so, in Idaho, the fruit of this labor very well may shrivel on the vine.

Oregon is a bit farther up the road of enlightenment. There the Brown Foundation pioneered in the production of excellent audiovisual material to be used in teaching about human sexuality at the elementary school level. The medical school in that state and the institutions of higher learning have had the foresight, and the leadership, to include health education as a major item in their curricula. The women of the Oregon Medical Association Auxiliary have made total health education, including sex education, from kindergarten to grade 12, one of their most sought after goals.

Oregon is indeed a progressive state, but even in that enlightened climate communities are still asking the citizenry to vote yes or no on whether to offer health education in the schools. Were we ever asked to vote on whether we should stamp out tuberculosis, or whether to immunize our children against polio?

The medical profession should not have to shoulder the full blame for not stemming the surge of this societal sickness that afflicts our younger generation. But we have done less well than we could have in this aspect of preventive medicine. For fear of being labeled as seamy sexologists we have kept our silence when we could have spoken out in our communities, to PTA's, to service clubs, to the general public. Today's parents are hoping for help. But because

we physicians feared rebuff, we have failed to offer our services to the school systems. And, we have missed opportunities (as did the IMA House of Delegates) to inform and influence our legislators, possibly under the misapprehension that it might be politically inopportune. Yet, this did not deter our California colleagues.

It is also probable that we, as individual physicians, have reneged on our responsibilities in this one area of preventive medicine, either because we felt unqualified by lack of learning, or because we were not comfortable in dealing with this sensitive subject. That excuse is no longer valid. Excellent courses are now everywhere available so that any of us can acquire a good working knowledge in human sexuality. And with knowledge we attain confidence and comfort.

Late word from Washington, DC, indicates that the Senate Human Resources Committee is marking up S2910, the "Adolescent Health Services and Pregnancy Prevention and Care Act." The stated purpose of S2910 is "to reduce unwanted initial and repeat pregnancies among teenage girls." What a pity we have to run to Washington for help when we can do a better job here at home.

No one expects us to effect a total cure of all teenage sex-related problems, but there is every indication that parents, churches, legislators, even educators, are looking to the medical profession to pick up our share of the responsibility. We hear loud cries for "health prevention" and "cost containment" from the politicians. Where can we make a better start than with the teenagers of America?

E. R. W. FOX, MD
Special Editor for Idaho
Coeur d'Alene, Idaho

Psychiatry and Psychotherapy

TO THE EDITOR: Contrary to Friedmann's argument (West J Med 129:156-159, Aug 1978) that psychiatry might leave the psychotherapeutic treatment of the severely disturbed in the hands of nonmedically trained psychotherapists, it seems more likely that nonmedical psychotherapists will have little or no role in the care of these patients as practical therapeutic applications are developed from recent advances in neurobiology.

Psychiatry today is at the threshold of a scientific revolution similar to medicine's experience in the late 19th century when the foundations for scientific medicine based upon bacteriology, biological chemistry and the systematic examination of diseased tissues were being discovered. Like psychiatry today, medicine then was divided along ideological lines; the various camps saw themselves as the respositories of the eternal verities of the healing process. With the spreading acceptance of an empirical approach to diagnosis and treatment, these ideological schools withered; the result is the medicine practiced today.

The significant finding of this early period in the emergence of scientific psychiatry is that the causes of the major mental disturbances are more complex than the total psychological explanations offered by the ideological schools. Neurobiology suggests significant genetic and biochemical implications. The understanding of these disturbances is further complicated by the tendency of the manifestations of these illnesses to be profoundly susceptible to coloring by the characteristics of the surrounding culture, and perhaps to the effects of current psychotherapeutic modalities and the welfare schemes designated to assist these sufferers.

The shift towards scientific psychiatry has changed the conception of what constitutes ideal treatment for the severely disturbed. Until about 20 years ago, the ideal was psychoanalysis in which patients were seen in individual treatment several times weekly. Medication was rarely used, symptomatic relief by medication being perceived as inimical to the healing process theorized to occur by insight. This system gave way to the present conception which combines psychotherapy with medication. Neither of these approaches has consistently led to fundamental cures in most patients with severe mental illness. The advantage of the newer combined method is a reduction for many patients in social pathology such that many can lead relatively independent lives free of the burdens of long-term hospital stays. The current system appears to be a compromise while awaiting definitive treatments. Because the monetary costs of these labor- and capital-intensive current treatments are extremely high, their future usefulness may depend more upon the national economic health than upon clinical outcomes.

Within the context of the emergence of scientific psychiatry, the fate of nonmedically trained psychotherapists might be the same as the physician ideologues of the late 19th century who were rendered obsolete by the march of medical prog-

ress. At the present primitive state of psychiatric knowledge, nonmedical psychotherapists might appear the relative equals of psychiatric physicians in the practice of psychotherapy. The same comparison could have been made between the first scientifically trained physicians and their ideological counterparts in the early days of modern medicine. Neither had much to offer patients aside from ineffective nostrums and bedside psychotherapy. The arrival of pathophysiological diagnosis and effective pharmacology caused the obsolesence of the physician ideologues and their schools. With no knowledge of scientific medicine, nor even the tools to learn it, they had little to offer but psychotherapy. However, a scientific physician was able to use psychotherapy in its most effective form, as a vehicle to gain his patient's cooperation to accept definitive treatment for hitherto untreatable diseases.

Similarly, nonmedical psychotherapists are likely to go the way of physician ideologues of the last century as the promise of definitive medical treatments for the severe mental disturbances is met.

MARK I. KLEIN, MD
Berkeley, California

Charter Tour Difficulties

To THE EDITOR: The Medical Society of Santa Barbara County, California, is having difficulty recouping travel deposits from an Ontario, Canada, consumer protection fund, and we would like to let other physicians realize our dilemma. We have been trying for more than 18 months to recover almost $88,000 lost when an Ottawa firm, Professional Seminar Consultants, Ltd. (PSC, Ltd.) defaulted on a charter tour of the Soviet Union.

Our medical society and three other professional groups have sued the Ontario Travel Industry Compensation Fund which rejected 96 American claims totaling $187,750, but approved claims of Canadian consumers against PSC, Ltd. for $150,000. The matter is now pending before the Ontario Commercial Registration Appeals Tribunal, with a decision expected by winter.

The Canadian licensing and investigatory authorities have refused to comment on the reasons for the thrice delayed denial of United States consumers' claims. We have attempted to apply pressure at the ambassadorial level with little success. At the request of Senator Alan Cranston, the Consulate General of the United States discussed the claims with the Registrar of the Travel Industry Act. The Registrar said that the Travel Industry Compensation Fund and its Board of Trustees' decisions are completely independent of the Government of Ontario and out of its control.

Meanwhile, there are 150 Californians, almost half from the tour sponsored by our Society, who are still out their monies. Our Society and its tour participants were assured that services were insured by the Travel Industry Compensation Fund. We find need for litigation appalling.

LEONARD A. PRICE, MD
President
Medical Society of Santa Barbara County
Santa Barbara, California

'Speed' and Hematuria

To THE EDITOR: Emergency room patients with microscopic hematuria and flank pain but no demonstrable renal stone are often suspected of seeking narcotics. An interesting, and potentially lethal, variation was seen at Kaiser Hospital, Hayward, California, recently.

A 21-year-old man came to the emergency room complaining of 24 to 48 hours of dull right flank pain. Analysis of urine showed no leukocytes or bacteria, but the specimen was "loaded" with red blood cells. Findings on intravenous pyelogram (IVP) were normal. Physical examination showed no abnormalities. Subsequent laboratory data showed a prothrombin time of 49 seconds (control 12.3); partial thromboplastin time, 48 seconds (control 34.9); platelets, 319, 000 per cu mm; hematocrit, 42 percent; creatinine, 1 mg per dl; serum glutamic oxaloacetic transaminase (SGOT), 30 units.

There was no family or personal history of bleeding problems; the patient had had a tonsillectomy and hernia correction without incident. There was no history of renal or hepatic disease.

The patient did have a new job, worked the graveyard shift and was using "speed," bought on the street, to stay awake. His girlfriend brought in the "speed," then identified as 10 mg Panwarfin® (warfarin sodium) (white tab with Abbott insignia). Sold Panwarfin as an "upper," he had been ingesting 30 mg a day for the previous three to four days. Treatment with vitamin K_1 corrected the laboratory abnormalities.

In view of this experience, perhaps prothrombin time should be checked to rule out unsuspected anticoagulant ingestion in all patients in whom findings on an IVP are normal, hematuria is present and use of street drugs is suspected.

BRUCE FRANKLIN, MD
Hayward, California

Refer to: Kitchen LW: Suicide among medical students (From a Medical Student). West J Med 129:441-442, Nov 1978

Suicide Among Medical Students

LYNN W. KITCHEN, MD, *Stamford, Connecticut*

FOLLOWING THE SUICIDE of a student at my medical school, a committee was created to "look into the psychiatric care of medical students." Along with my fellow classmates, I received a letter from the committee chairman: would I be willing to share some of my first-hand experiences and observations on medical school "stresses"?

As long as suicide remains the second most common cause of death among medical students in the United States,[1] the question of motive deserves careful attention. But I suggest that we should be very cautious about making the leap from the fact of incidence to the notion (implicit in the phraseology of the inquiry sent to my class, and explicit in much of the discussion preceding the launching of the project) that "academic and personal stress" and "unsuitability for the profession" explain why medical students destroy themselves.

In the first place, the statistics are not conclusive. While a study published in 1968 found the suicide rate among 85,299 students attending 50 medical schools in the United States between 1947 and 1967 to be "significantly higher" than among controls matched for age, sex, race and residence,[1] the director of a similar study underway in 1978 hazards the prediction that his final findings will not show any noteworthy discrepancy between the suicide rate of medical students in the United States and the control group (interview with Don A. Rockwell, MD, Department of Psychiatry, University of California, Davis, School of Medicine, June 1978). In any case, the suicide rate among graduate MD's—at least 100 per year in the United States—is almost certainly higher than that among medical students.[2] This suggests to me that we ought to be giving primary consideration to factors common to self-destructive student and graduate physicians. Could the suicidal persons among the two groups have more difficulty than their peers in coming to terms with the issue of their own mortality?[3]

Although it is part of the mythology of the medical profession that many of those who are motivated to undertake the study of medicine suffered serious personal illness as children or witnessed this phenomenon in another family member, I have encountered difficulty in documenting this in available literature. Moreover, my empirical conclusion based on four years of medical school has been that student physicians adjust surprisingly smoothly to our daily encounters with the ravages of incurable diseases on our patients. Halberstam's perceptive observation of us was that "far from becoming fixated on the pathology they study, they are likely to have considerable difficulty making any [overt] emotional connection between the patients they examine . . . and the inevitable deterioration of their own bodies."[4]

There are at least five good reasons why this is so. First, medical students tend to be a young, energetic, physically robust group, with a sense of much useful work and productivity ahead of them. Second, lulled by the tidying, elegant phrases of the "voices of experience" on rounds, we exhaust ourselves in our quest to be perfect. Even as we scoff at the godly ways of our mentors, we gradually and unconsiously come to emulate their assured posturing. Third, in the early stages of training, student physicians rarely have long-term relationships with those they treat —in part because of the frequency of rotations, but also because so many patients in teaching hospitals are likely to be self-abusing and therefore not particularly likable persons. Fourth, the attending physicians attracted to academic medicine are often research-oriented rather than patient-oriented, by which I mean that empathetic clinical role models are sometimes the exception rather than the rule. Fifth, should personal feelings about the death of a patient become troublesome, a student physician has the support of his

The author was a fourth-year medical student, Class of 1978, University of California, Davis, School of Medicine, when the article was submitted. She is now an intern in the Department of Medicine, Stamford Hospital, Stamford, Connecticut.

Reprint requests to: Lynn W. Kitchen, MD, Dept. of Medicine, Stamford Hospital, Shelburne Road and West Broad Street, Stamford, CT 06902.

team in developing and utilizing his defenses to deal with the loss. (It strikes me as significant that it is not at the student level but when these buffers are taken away that the suicide rate is highest—that is, among physicians in practice long enough to have been made painfully aware that medicine is a frontier art as a result of the deaths of parents, siblings, respected colleagues and patients who have become friends.[5])

In sum, I believe that we are on the wrong track in approaching the incidence of suicide in our profession as a problem that has an answer, and I doubt that many prospective suicidal persons can be somehow weeded out at the medical school admissions level.[6,7] Ernst Becker, in his brilliant work *The Denial of Death,* characterized guilt and depression as the natural consequences of coming to terms with one's vulnerabilities.[8] Indeed, suicidal tendencies in all persons usually follow some blow in self-esteem—whether in the area of interpersonal relationships, examination grades, or failing physical health. To the degree that the medical student and the physician he becomes is ruled by the demanding value system passed on from generation to generation in the medical profession, no amount of achievement will spare him from guilt at not being all that he has been conditioned to expect of himself. And what is suicidal ideation if it is not the aspiration to kill off the unfulfilled aspects of oneself, the aspects that render one inescapably imperfect, mortal? Perhaps the suicidal person's unconscious fantasy is that he will be able to exorcise his failures via the self-destructive act, but somehow survive to profit by this; he may be too angry—at his imperfect self and at a world which he views as demanding absolute perfection—to consider the finality of death.[9]

"Suicide," in the words of Camus, "is prepared within the silence of the heart."[10] This is likely to be especially true for those shaped according to a professional ethos that emphasizes the playing out of godly roles and discourages admissions (even to oneself, let alone a possible counsellor) of uncertainty or imperfection. Whether or not a person who experiences suicidal ideation actually chooses to kill himself depends on such factors as his insight, his ability to concede and explore his psychic pain, and his willingness (and luck) in establishing emotional intimacy with a psychotherapist or friend with whom he does not have to play charades.

Any malady quietly acknowledged and experienced—not compartmentalized, denied, or intellectualized away by the sufferer or those around him—becomes more manageable and bearable with time. Accordingly, the most reliable prophylactic against suicidal depression is to be found in the lonely, lifelong task of coming to grips with one's limitations and mortality, with what one can and cannot control in his life. It follows that the most productive way of discouraging self-destructive tendencies in medical students is to encourage them from the beginning of their training to embrace their humanity.

The issues of suicide, death, dying and personal vulnerability ideally should not be delegated (with obvious implications) to departments of psychiatry, but dealt with by physician role models at all levels of the medical school hierarchy on a day-to-day basis. Too, more exploration in the medical school curricula of the therapeutic possibilities—for both parties—engendered by a solid doctor-patient relationship is warranted. For to the degree that the physician can derive satisfaction from his patients' faith in him as an empathetic, mature, competent person "on their side" of the battle, and utilize this faith as a potent healing tool, he will be better able to withstand his disappointment—whether experienced within himself or voiced by others—over human errors and his inability to perform "miracles."[11]

These measures could result in a lowering of the suicide rate not only among student but also among graduate physicians. There is only one liberty, wrote Camus in his *Notebooks:* "to come to terms with death. After which, everything is possible."

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Special Article

The Duty of Hospitals and Hospital Medical Staffs to Regulate the Quality of Patient Care

B. ABBOTT GOLDBERG, LLB, *Sacramento, California*

In 1881 Oliver Wendell Holmes, Jr. wrote: "The life of the law has not been logic; it has been experience."[1] Holmes went on to become the "great dissenter."

His father was Dr. Oliver Wendell Homes, Sr., once dean of the Harvard Medical School. In 1842, almost a generation before Semmelweis, Dr. Holmes published a paper, "The Contagiousness of Puerperal Fever," which held that the disease was related to the personal uncleanliness of the attending obstetricians.[2] The medical profession rose up in arms against Dr. Holmes. He ignited a controversy that would rage for years. One of Dr. Holmes' opponents was Dr. Hugh Lenox Hodge, professor of obstetrics at the University of Pennsylvania and the Pennsylvania Hospital. That hospital's department of obstetrics "had a somewhat unfortunate experience with puerperal fever and after being closed for some time was finally abandoned in 1854."[3]

Dr. Holmes replied to his critics only rarely. But he did say once: "I am too much in earnest for either humility or vanity, but I do entreat those who hold the keys of life and death to listen to me for this once. . . . I beg to be heard in behalf of those . . . whose lives are at stake, until some stronger voice shall plead for them."[4]

The author is a retired judge of The Superior Court, Sacramento, California.

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Reprint requests to: B. Abbott Goldberg, Judge of The Superior Court, Retired, 3221 American River Drive, Sacramento, CA 95825.

The statements of both Dr. Holmes and Justice Holmes epitomize the theme of this discussion. Improvement in the quality of patient care cannot be accomplished by law alone. The law is too variable, too subject to historical accidents and to the transitory sentiments and prejudices that judges share with their fellow men, to provide any lasting assurance. Real assurance of improvement in the quality of care can be provided only by constant dedication to that goal by those "who hold the keys to life and death." Such dedication may require the sacrificing of some sacred cows, a prospect that not everyone can face with the equanimity of a Dr. Holmes.

The Nork Case

My introduction to the questions of hospital and medical staff liability for the quality of patient care was in 1973 in a notorious malpractice case, *Gonzales vs Nork and Mercy Hospital.*[5]

Dr. John Nork performed a laminectomy on Gonzales at Mercy Hospital in Sacramento in November 1967. Dr. Nork had hospital staff privileges to do orthopedic surgery, including laminectomies and spinal fusions. There was evidence that before Gonzales' surgery, Dr. Nork had performed some 13 other laminectomies or fusions at the same hospital, with poor results. His patients suffered grave postsurgical complications, such as arachnoiditis, causalgia, foot drops, bowel and urinary incontinence, and sexual disabilities. One patient suffered a vertebral fracture during surgery. Several required repeated

surgeries, as many as four times. In one nonspinal case, a woman lost a leg as a result of repeated bone grafts on an ankle, in the presence of infection.

The hospital was accredited by the Joint Commission on Accreditation of Hospitals, and it maintained all the relevant committees—such as tissue, infection, utilization and surgical. All of these committees reviewed cases in the then standard manner, but these standard reviews failed to reveal the doctor's lack of skill. At the time of Gonzales' operation, the hospital had no actual knowledge of Dr. Nork's incompetence or of his practices of operating on inadequate findings and falsifying hospital records. A recurrent theme in the case was how such medical misconduct could occur and remain undetected in a well-ordered hospital.

The case was tried against Dr. Nork on the bases of both fraud and negligence, but against the hospital on negligence only. The hospital contended that it was not responsible for the conduct of the physicians on its staff, because they were not its agents, employees or servants. This contention is correct. A hospital is not liable under the doctrine of "respondeat superior" merely because a staff doctor is negligent.[6] The Latin expression respondeat superior is legal shorthand for the rule that a principal, employer or master—the superior—is responsible for the torts of his agent, employee or servant committed within the scope of the subordinate's employment. This rule applies even though the superior himself is free of fault. The rule is centuries old, and its justification is that the superior can spread the risks of loss, by insurance or otherwise, as part of the cost of doing business.[7] Respondeat superior had no direct bearing on this case, because the doctor was not an employee of the hospital, but it is peculiarly significant in the development of the law relative to hospital liability.

If a staff doctor is not an employee, what is he? In conventional legal terminology, one is either an employee or an independent contractor. An employer is liable for the torts of the employee, but, subject to very broad qualifications, not for those of an independent contractor.[8] Although a staff doctor is an independent contractor, he is also a concessionaire or licensee, a person to whom the hospital grants the privilege of practicing medicine within the hospital's premises. The hospital is the occupier of land on which it invites patients into its custody, for treatment by its concessionaires. By granting staff privileges and by taking custody of patients, the hospital incurs the risk of liability for torts committed by the concessionaire, the staff physician, without regard to his status as an employee or independent contractor—if the hospital is subject to the same rules as every other grantor or custodian.

What are the rules applicable to every other grantor of a concession or custodian? In brief, there is but one rule, and that is to use due care to see that those in custody are not harmed and that the concessionaire does not harm the grantor's customers.[8] The application of the rule can be illustrated by a variety of examples: the common carrier held liable for rape because it allowed a woman to alight at a point known to be frequented by ruffians;* the tavern keeper held liable for battery because he did not protect a patron from a beating by a drunk;[10] the amusement park operator held liable for inattention to the operations of roller coasters or fireworks displays conducted by independent contractors.[8,11] On principle, it is undeniable that a hospital owes at least as great a duty of care to a patient to protect him from an incompetent doctor as a railroad does to a passenger, or a barkeeper to a patron or an amusement park owner to a spectator.

Genesis of Hospitals' Liability

Thus the question is whether hospitals are subject to the same rules as everyone else. To answer this question, it is necessary to look to history. As Justice Holmes said: "In order to know what it [the law] is, we must know what it has been, and what it tends to become."[1]

Originally there were no special rules exempting hospitals from the rules applicable to everyone else. Under common law, all charities were immune from liability for the negligent acts of their subordinates.[12] Since most hospitals were charities, they, too, enjoyed this general charitable immunity. So special rules for hospitals had to be developed either in cases of noncharitable hospitals,[13] a category of no practical importance to this discussion, or in cases involving intentional, as distinguished from negligent, torts. The latter category was involved in a case of utmost historical importance, *Schloendorff vs Society of New York Hospital.*[14]

*Reference 8, §§314A, 318, 320, 344, 415, 419, 447, 449 (Illustration 1); Reference 9

Schloendorff is the archetypical case, decided in 1914 by the late, great Benjamin Nathan Cardozo. It held flatly that a hospital is not liable for the acts of doctors, whether they are agents, "house physicians," or are staff members, "visiting physicians." The plaintiff alleged that two doctors, one a "house physician," and the other a "visiting physician," both procured for her by the hospital, operated on her without her consent. If true, this amounted to a battery, an intentional tort. Judge Cardozo held that the plaintiff's "narrative, even if improbable must be taken as true" and "that the relation between a hospital and its physicians is not that of master and servant. The hospital does not undertake to act through them but merely to procure them to act upon their own responsibility." This is the genesis of the rule that hospitals were not liable for the acts even of those doctors whom they employed—the rule exempting them from the general rule of respondeat superior. This exemption was never adopted in California.[15]

Other language in the opinion resulted in at least two other rules, which gained wide acceptance for many years: First, the "borrowed servant" rule, that a hospital is not liable for the acts of its acknowledged servants, such as nurses, if they are acting under the direction of the doctor. They became for the time being the servants of the doctor rather than the hospital. California never adopted this rule, either. Instead it has applied the rule of respondeat superior to both the doctor and the hospital.[16,17] The second rule is that the administrative or housekeeping activities of a hospital must be distinguished from its medical activities, the hospital being liable for the one as any other innkeeper, but not for the other because they were performed through doctors. Although *Schloendorff* was expressly called to its attention in 1945, the California Supreme Court rejected this medical-administrative dichotomy and held, following its own precedents: "a nurse or physician may be the servant of a hospital, thus requiring the application of the doctrine of respondeat superior even though they are performing professional acts."[18]

To recapitulate: *Schloendorff* held that a hospital was not liable for the acts of a doctor because the doctor could not be its servant. If the hospital was not liable under respondeat superior, clearly it was not liable for the acts of a doctor who was merely an independent contractor, or licensee or concessionaire. But at the time *Gonzales vs Mercy Hospital* arose, the question was not what the rules were under *Schloendorff,* but whether those rules were still viable. They had little vitality in California; did they have any? There is still no authoritative answer in California,[19] but I held it to be *no.*

Enter the ACS

The first erosion I found in *Schloendorff's* concept that a doctor in a hospital acts solely on his own responsibility is not in any legal material but rather in the history of the American College of Surgeons. The college was an effort to create an organization "devoted completely to the evaluation of professional and hospital standards which would benefit the patient."[20] In 1919, while *Schloendorff* was in full bloom, the college adopted its "minimum standard," stating that each hospital should have an organized staff of competent physicians who would adopt rules governing their professional work and who would "review and analyze at regular intervals their clinical experience."[20(pp221,489)]

The minimum standard was adopted over stiff opposition. It was argued, parallel to Judge Cardozo's thinking, that a hospital was simply a more convenient place to operate than a home. "The hospital's sole obligation was to furnish space with proper heat, light and food for the patient. When these services were paid for by the patient and he was discharged, the hospital's interest and obligation to the patient ceased." Staff meetings were assailed as impositions on busy doctors. Operation reports were an invasion of the patient's privacy.[20(p205)] Only 89 of 692 hospitals surveyed could completely meet even the simplest requirements. The printed report reciting this embarrassing statistic was suppressed and copies naming the hospitals were destroyed.[20(p221)]

Nevertheless, the minimum standard was adopted as a "goal to seek."[20(p221)] The goal was "to standardize hospitals in such a way that the public could know to which hospitals they could go with safety."[20(pp63,475-476)] It was to be reached by having organized medical staffs that would "adopt rules, regulations and policies which would insure the best possible service to the patient."[20(p221)]

As early as 1913 Dr. Ernest Codman of Boston was urging the "common sense notion that every hospital should follow every patient it treats, long enough to determine whether or not the treatment

has been successful and then to inquire if not, why not?"[20(p116)] (Note: Dr. Codman thought the hospital treated the patient; a year later Judge Cardozo thought it did not.)

The minimum standard's single page became the progenitor of the Joint Commission on the Accreditation of Hospitals' Accreditation Manual and, in 1965, of California Business and Professions Code §2392.5, where parts of it survive verbatim. It is important because it shows how the surgeons were acting to improve hospitals, as a matter of the proper practice of medicine, without legal stimulus, because for many years thereafter the law relieved hospitals of liability for physicians' conduct.

Schloendorff did not receive its legal coup de grace until 1957, when the New York Court of Appeal, in *Bing vs Thunig,*[21] held a hospital liable for the negligence of a nurse who burned a patient during a surgical operation. The nurse was not acting under the particular direction of a physician. Nevertheless, the hospital argued that her conduct had to be characterized as "medical" rather than "administrative," so the hospital should not be liable. The court found this dichotomy riddled with unworkable, quixotic distinctions and abandoned it. In so doing, it reconsidered *Schloendorff* and put to itself the question: "What reason compels us to say that of all employees working in their employers' business . . . the only ones for whom the employers can escape liability are employees of hospitals?"[21] It answered its own question by first repudiating Judge Cardozo's proposition that "the hospital does not undertake to treat the patient, does not undertake to act through its doctors and nurses, but undertakes instead simply to procure them to act upon their own responsibility." This conception, said the New York court, "no longer reflects the fact. . . . Certainly, the person who [now] avails himself of 'hospital facilities' expects that the hospital will attempt to cure him, not that its nurses or other employees will act on their own responsibility." It then held:

> Hospitals should, in short, shoulder the responsibilities borne by everyone else. There is no reason to continue their exemption from the universal rule of respondeat superior.[21]

Thus *Schloendorff* was interred after 43 years of troubled existence.

The Darling Case

But *Bing vs Thunig* involved an admitted employee and did not itself answer the question of whether a hospital was liable for the acts of a nonemployee, a staff physician. However, its language implied the answer, and that implication was followed in the case of *Darling vs Charleston Comm. Mem. Hosp.,* decided by the Illinois Supreme Court in 1967.[22] *Darling* held a hospital liable because it had not required a doctor to follow the hospital's own rules. "Although the legal doctrines expounded in the *Darling* case were neither new nor novel, the application of these doctrines to the medical staff setting . . . gave the case widespread publicity, and shock value."[23]

Although *Darling* is the famous case, one even more instructive is *Fiorentino vs Wegner.*[24] *Fiorentino* involved a death resulting from a novel surgical procedure performed by a nonemployee staff physician. It held that the hospital was not liable, because the procedure, although novel, was not "per se an act of malpractice," and the hospital had "no reason to know that an act of malpractice would take place." What is important in *Fiorentino* is not its result but its statement of the law.

> [A] hospital will not be held liable for an act of malpractice performed by an independently retained healer, unless it had reason to know that an act of malpractice would take place. . . . [A hospital] is not required to pass upon the efficacy of treatment; it may not decide for a doctor whether an operation is necessary, or, if one be necessary, the nature thereof; but it owes to every patient whom it admits the duy of saving him from an illegal operation or false, fraudulent, or fictitious medical treatment. . . . [L]iability does not attach to the hospital unless it knew or should have known that . . . the operation was not permissible under existing standards.[24]

The key thought in this quotation is what the hospital "knew or should have known." This had already been stated in *Darling.*[22] It was developed in 1970 by the Nebraska Supreme Court in *Foley vs Bishop Clarkson Memorial Hospital.*[25] If the liability of a hospital were restricted to cases where it had actual knowledge, carelessness would be promoted, for "the less a hospital [knew] about a patient's condition, the safer it [would be] against charges of negligence." The Nebraska court stated that the majority rule applied by most states in hospital cases requires actual knowledge, but that this majority rule "is an exception to the general law of negligence." It then applied what it

called the minority rule derived from *Darling,* rejected the majority rule, and overruled prior Nebraska cases. Thus, without citing *Bing vs Thunig,* Nebraska aligned itself with the New York philosophy that "Hospitals should . . . shoulder the responsibilities borne by everyone else."

A further application of general law to hospitals is that a hospital cannot escape liability merely by doing what all other hospitals are doing. This application of the general law to hospitals was mentioned in *Darling.*[22] It has been the law in California since 1956, when the California Supreme Court held in an instrument-count case: "Although . . . practice or custom is some evidence of what should be done and may assist in the determination of what constitutes due care, it does not conclusively establish the standard of care."[26] Thus in 1973, (1) the hospital no longer enjoyed a special exemption from general tort liability; (2) liability could result from a failure to follow its own rules; (3) liability could result from a negligent failure to know what its staff doctors were doing, and (4) the fact that the hospital was doing exactly what a hospital approved by the Joint Commission on the Accreditation of Hospitals (JCAH) should have done did not necessarily prove it was not negligent. With these propositions in mind, I shall develop some of the facts of *Gonzales vs Mercy Hospital.*

Nork: The Hospital's Failures

There were instances of violations of rules shown in the case, not with reference to Gonzales as a patient as in *Darling,* but with reference to failure to apprehend Dr. Nork before he operated on Gonzales. For example, in one prior instance, the hospital pathologist violated an express rule requiring him to report tissue discrepancies; he failed to report to the Tissue Committee that Dr. Nork had removed nerve fibers during a laminectomy.[5(p150),27] In another case, the nursing staff failed to report that Dr. Nork allowed his assistant surgeon to leave shortly after a laminectomy was begun and required a surgical nurse to function as assistant surgeon.[5(p192),28] There were other unreported or uninvestigated cases, such as unduly protracted hospitalization, infection and unexplained discrepancy between admitting and discharge diagnoses. Had these been explored, Dr. Nork's deficiencies might have been disclosed and acted on much earlier—and prevented his operation on Gonzales. Whether such protective action would have been taken presented a difficult problem of proximate or legal causation, which distinguished Gonzales' case from *Darling.*[28(p130)]

To avoid the distinction between *Darling* and Gonzales' case on this question of causation, I adopted the approach of *Fiorentino vs Wegner* that a hospital has a duty to save a patient from false or fraudulent medical treatment of which it knew or should have known. From this it follows that a hospital must maintain reasonable means of acquiring such knowledge. But in 1967, the relevant period, the hospital not only lacked knowledge of Dr. Nork's propensities, it had no means of acquiring it.

Although in 1967 the hospital did follow all of the procedures required by JCAH, those procedures were insufficient to detect an inadequate physician such as Dr. Nork. Dr. Reed M. Nesbit, the hospital's principal witness, said it may take a malpractice case to detect such a doctor.[5(p145)] Dr. Nesbit is professor emeritus of urology at the University of Michigan, a former president of the American College of Surgeons, a former member of the Joint Commission and, at the time he testified, was Deputy Director of the Commission. He was involved in the case because JCAH wanted to find out how it had approved a hospital where such conduct had occurred. In his own words: "It was incredible to me that the allegations were such as they were [and] that some of the people on the medical staff didn't pick up something on the guy."[5(pp143-145)]

Shortcomings of JCAH Standards

The testimony of Dr. Nesbit showed that the JCAH standards, which the hospital was following in 1967 as far as the records showed, and their application were deficient in the following respects:

1. The review of cases was predicated on the assumptions that the doctor was reporting honestly and that the records were truthful and accurate. Such assumptions preclude the possibility of discovering fraud.

2. The assumption of honest reporting was carried so far that no comparison of the doctor's progress notes and the nurses' notes was either required or made.

3. The clinical review was subjective and according to the personal standards of the reviewer. As an experiment in court, a highly regarded

neurosurgeon reviewed five of Dr. Nork's hospital files the way he would have reviewed them in the hospital in 1967. Giving himself the same time limitations that he was under in the hospital, he could not discover even the grossest deficiency: that all the patients had the same or similar patterns of detailed symptoms. This pattern arrangement of symptoms becomes readily detectable only by setting them forth in tabular form. This simple mode of arraying the symptoms was a device hit upon by the plaintiff's counsel, following a suggestion of his orthopedic expert. Merely by assembling and analyzing the evidence objectively, a lawyer rather than the doctors discovered that Dr. Nork had been contriving his findings.[29]

4. The review was based on random sampling of cases in selected areas. Therefore, bad cases were picked up only by chance. To quote Dr. Nesbit: "It is very difficult to get an accurate picture from a random sample on a random sample basis."[5(pp174-182)]

5. The review was infrequent. In Dr. Nesbit's opinion, such infrequent review "emphasizes the randomness, if you will, of the sampling."[30] On this point, Dr. Nesbit distinguished between teaching hospitals—those having interns and residents—and hospitals without such programs. In a teaching hospital, review is current and frequent, rather than retrospective and rare, and the review does not have to assume the truthfulness of reports by the attending physician as the sole witness, because the patient is under the multiple observation of several witnesses, even though they are students.

6. The review process was casual, hasty and sandwiched between the reviewing doctor's other work.

7. Finally, but equally important, no protocol, profile or record was made of the deficiencies of the doctor being reviewed, so there was no common fund of such knowledge about the doctor available to the hospital.[5(p183)]

Adherence to a review system so riddled with inadequacies could not properly be held to comport to a standard of due care. How the review system can be improved and which among various improvements is the best is a subject better left to those most competent and knowledgeable in this field. However, it should be observed that the "Procedure for Retrospective Patient Care Audit In Hospitals," proposed by the Joint Commission in its Trustee, Administrator, Physician Institutes in 1973, is vastly more effective than any of the prior procedures that were placed in evidence in the Gonzales case.

Additional Liability Potential

There is another possible phase of liability. The failure of the hospital medical staff to discover and disclose Dr. Nork's deficiencies raises the possibility that staff members with reviewing responsibilities, who negligently allow a deficient doctor to remain on the staff, may themselves be held individually liable to the patients that the doctor injures.

A formidable argument can be made in favor of the theory that members of the medical staff who negligently fail to detect an incompetent staff member may themselves incur liability to the incompetent's patients even though there was no physician-patient relationship. The absence of the relationship is, in legal terms, called a "lack of privity." But privity is not an essential basis of tort liability. The American Law Institute, whose Restatements of the Law are generally considered authoritative, says in part:

> One who undertakes . . . [the medical staff] to render services to another [the hospital] which he [the medical staff] should recognize as necessary for the protection of a third person [the patient] . . . is subject to liability to the third person [the patient] for physical harm resulting from his [the medical staff's] failure to exercise reasonable care to [perform] his undertaking. . . .[31]

This rule has been applied in a hospital context.[32] A patient was injured when she fell into a bathtub because she was frightened when a rat ran across her feet. She sued the hospital and hospital's exterminator. (The implicit analogy of an incompetent doctor to a rat and a medical staff to a pest exterminator is only a coincidence, not a reflection of personal animus.) The United States Court of Appeal held that both the hospital and the exterminator could be liable. The exterminator had never heard of the patient, but the court held the absence of a prior relationship immaterial, because the section of the Restatement of Torts "renders the defense of lack of privity unavailable. . . ."[32,33]

The critical issue is not the presence or absence of privity; it is whether the medical staff has undertaken a duty to the hospital to protect the hospital's patients from incompetents. That it has can be argued in at least three ways:

1. From the statute, Business & Professions Code §2392.5. This statute is in part a paraphrase

and in part a verbatim adoption of the old "minimum standard." In form it is a definition of one sort of unprofessional practice; that is, practicing in a hospital without a formal medical staff. Considering its origin and form, it seems clear that the statute was intended not only to regulate relations between hospitals and doctors but also to benefit hospital patients.

2. For hospitals accredited by the Joint Commission, the conclusion follows from inspection of the Accreditation Manual for Hospitals. The foreword to the manual states that the certificate of accreditation should be a matter "of reassurance to [the hospital's] patients." This reassurance should follow from the medical staff's duty to "maintain continuing surveillance of the professional performance of all members of the medical staff" and to establish "criteria for evaluating medical care" that should be "strict enough to safeguard patients." When a doctor becomes a staff member, "he accepts medical staff controls as a protection to himself as well as to others."[34] Who these "others" are is clarified by the standard that requires "meetings to review the clinical work of members . . . because the medical staff has overall responsibility for the provision of medical care to patients."[34] If the word "others" did not include all hospital patients, the references to safeguarding and reassuring patients would be but idle ornamentation.

3. The conclusion follows from medical staff bylaws—for example, those of the University of California in San Francisco. The preamble recognizes "that the Medical Staff is responsible for the quality of medical care in the Hospitals and Clinics and must accept and assume this responsibility . . . and that the best interests of patient care are protected by concerted effort. . . ."[35] The Patient Care Review Committee is "responsible for insuring that the medical care provided . . . is appropriate, of reasonable quality, and provided in an efficient manner."[35] Its Medical Care Review Subcommittee is required to help the departments develop "quality care standards, along with appropriate mechanisms to monitor the implementation of these standards in actual practice."[35] These rules implement the Principles of Medical Ethics, which require physicians to "safeguard the public . . . against physicians deficient in . . . professional competence." By accepting staff membership, doctors have voluntarily undertaken responsibilities to patients of other doctors, which they must discharge with reasonable care.[36]

I have found only one reported decision on the question of personal liability of medical staff members, *Corleto vs Shore Memorial Hospital*[37] decided by the Superior Court in New Jersey in 1975. *Corleto* held that a plaintiff who alleged injuries from surgery performed by an incompetent doctor could sue some 141 hospital staff doctors, the hospital administrator, the hospital board of directors and the hospital itself for their alleged negligence in allowing the incompetent to remain on the staff. *Corleto* is the straw in the wind indicating how far liability may be extended.

Proving the Hospital Remiss

The difficult problem is not establishing the existence of liability. The difficult problem is the factual one of obtaining evidence that a hospital, its medical staff and its administrator have been remiss in their duties by failing to discover and eliminate incompetent doctors. This was not a great problem in *Gonzales vs Mercy Hospital,* because circumstantial proof of staff derelictions became available by piecing together the evidence in the charts of some 30 of Dr. Nork's patients. But in a less exaggerated case, the problem may be formidable.

A number of states have enacted legislation intended to encourage adequate staff reviews by making the records and proceedings of such reviews either nondiscoverable or not usable in evidence, or both. These statutes are said to:

> Evince a legislative judgment that the quality of in-hospital medical practice will be elevated by armoring staff inquiries with a measure of confidentiality. This confidentiality exacts a social cost, because it impairs malpractice plaintiffs' access to evidence. . . . [Such statutes] represent a legislative choice between competing public concerns. [They] embrace the goal of medical staff candor at the cost of impairing plaintiff's access to evidence.[38]

The presence of such statutes underscores the theme at the outset of this discussion, that "The life of the law has not been logic; it has been experience." While the courts have been enlarging the scope of liability, the legislatures have been making liability harder to establish. These contrary movements may seem paradoxical, but they are not unusual. Justice Holmes said: "The truth is that the law is always approaching, and never reaching consistency."[1(p36)] He was unduly optimistic; sometimes it is not even approaching.

The existence of such "protective" statutes and the proliferation of similar statutes ameliorating

responsibility for medical malpractice and making malpractice actions more difficult to pursue[39] supports the reality that improvement of the quality of care lies with those "who hold the keys to life and death." Statutes give physicians privileges not enjoyed by other litigants, and it is up to physicians to be worthy of those privileges. A legislature could repeal the privileges if it believed they were abused. Further, there is some suggestion that the courts are skeptical of hospital and medical agency disciplinary proceedings.[40]

Resolving the Liability Problem

The liability of hospitals is, of course, part of the more general problem of the "malpractice crisis." There are various ways of resolving the crisis. To the late Dr. Paul Dudley White is attributed the statement: "The way to cut down the cost of malpractice insurance is to cut down the malpractice."[41] Dr. White's meaning seems clear. Actually it is ambiguous, because one way to cut down malpractice is to lower the standards of care, so that fewer injuries become legally actionable. For example, since a hospital may be liable for violating its own rules, it might attempt to avoid liability by having no rules. James E. Ludlam, legal counsel for the California Hospital Association, considered this possibility and rejected it. He referred a United States Senate committee to:

> hospitals that transferred the responsibility for the routine ordering of bed rails from the attending physicians to the nursing staff. This greatly reduced the number of injuries to patients, but from the point of view of limiting liability this was a major mistake by the hospitals. However, it did mean better patient care. . . . Insurability is not determined by losses but by devotion to the professional approach to better patient care.[17(p1060)]

In short, take care of the patient, and the liability will take care of itself.

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1. Holmes O Jr: The Common Law 1 (1881)

2. 26 Encyclopedia Americana, Surgery 63 (1972)

3. 9 Dictionary of American Biography 99 (1932)

4. Bowen C: Yankee From Olympus 88-89, 108 (1944)

5. Sacramento Superior Court No. 228566, Memorandum of Decision filed November 27, 1973. Dr. Nork appealed unsuccessfully on the ground that he had been improperly denied a jury trial, Gonzales vs Nork, 20 CA 3d 500, 143 Cal Rptr 240, 573 P. 2d 458 (1978), but successfully on his claim that the damages had not been correctly determined, Gonzales vs Nork, 3d Appellate District No. 15152, June 30, 1978, as modified July 26, 1978 (unpublished opinions). Mercy Hospital did not appeal and the case is final as to it. This paper is to be understood as relating only to the case against the hospital. For a discussion of the impact of the trial court decision see Law S, Polan S: Pain & Profit—The Politics of Malpractice. New York, Harper and Row, 1978, pp 58-67.

6. Mayers vs Litow, 154 CA 2d 413, 1957

7. Hinman vs Westinghouse Elec. Co., 2 C 3d 956, 959-60, 1970. For other references to availability of insurance in allocating liability, see Escola vs Coca Cola Bottling Co., 24 C 2d 453, 462, 1944; Bing vs Thunig, 2 NY 2d 656, 143 N.E. 2d 3, 7, 1957; Prosser & Wade, Cases and Materials on Torts 621 (1971).

8. Restatement (Second) of Torts §409 (1965)

9. Eg, Westwater vs Southern Pacific Co., 38 CA 2d 369, 371, 1940. For references to hospital liability in terms of general law, see Guilliams vs Hollywood Hospital, 18 C 2d 97, 99, 102, 1941, and Ybarra vs Spangard, 25 C 2d 486, 491-92, 1944.

10. Vesely vs Sager, 5 C 3d 153, 164, 1971; Winn vs Holmes, 143 CA 2d 501, 504-05, 1956

11. 2 F. Harper & F. James, Torts §27.19 at 1526 (1956); Ref 8, §§344 and 415

12. Restatement of Torts §887, Comment *c* (1939) (partial immunity). Malloy vs Fong, 37 C 2d 356, 367, 1951 (charity liable to nonpaying beneficiary). *A fortiori* a charitable hospital is liable to a paying beneficiary. Silva vs Providence Hospital of Oakland, 14 C 2 762, 776, 1939

13. Brown vs La Societe Francaise, 138 C 475, 1903 (ordinary rule of respondeat superior applied)

14. 211 NY 125, 105 N.E. 92, 52 L.R.A. (N.S.) 505 (1914)

15. Beeck vs Tucson General Hospital, 500 P. 2d 1153, 1155 (Ariz App 1972) (reviews the history and expressly rejects Schloendorff). Some California cases reject it implicitly: eg, Quintal vs Laurel Grove Hospital, 62 C 2d 154, 167-68, 1964; Seneris vs Haas, 45 C 2d 811, 831, 1956; Rice vs California Lutheran Hospital, 27 C 2d 296, 304, 1945.

16. Rice vs California Lutheran Hospital, 27 C 2d 296, 304, 1945 seemed to leave the point open. But the possible liability of both the hospital and doctor was recognized both before and after Rice. Ybarra vs Spangard, 25 C 2d 486, 492, 1945; Mundt vs Alta Bates Hospital, 223 CA 2d 413, 423, 1963. Several cases have held hospitals liable for medical acts of nurses: eg, Leonard vs Watsonville Community Hospital, 47 C 2d 509, 520, 1956; Cline vs Lund, 31 CA 3d 755, 763, 1973; Valentin vs La Societe Francaise, 76 CA 2d 1, 7, 1946.

17. See generally Sen. Comm. on Government Operations, 91st Cong., 1st Sess., Medical Malpractice: The Patient Versus the Physician, 435, 492-93 (Comm. Print 1969), "The Ribicoff Report"

18. Rice vs California Lutheran Hospital, 27 C 2d 296, 304, 1945. An analogous distinction between "professional malpractice" and "ordinary negligence" appeared, disappeared and briefly reappeared as to the statute of limitations. Gopaul vs Herrick Memorial Hospital, 38 CA 3d 1002, 1974: Zelver vs Sequoia Hospital District, 87 Cal Rep 79, 1970 (hearing granted but not thereafter decided).

19. Matchett vs Superior Court, 40 CA 3d 623, 629 n. 4, 1974

20. L. Davis, Fellowship of Surgeons—A History of the American College of Surgeons. 1960, p 204

21. 2 NY 2d 656, 143 N.E. 2d 3 (1957)

22. 33 Ill 2d 326, 211 N.E. 2d 253, 14 A.L.R. 3d 860 (1966)

23. Ludlam J: Physician-Hospital Relations: The Role of Staff Privileges. 35 Law & Contemp Prob 879, 884 (1970). For further remarks by the same author see Ref 17 (p 1060).

24. 19 NY 2d 407, 227 N.E. 2d 296 (1967)

25. 173 N.W. 2d 881, 884 (Neb. 1970); Ref 5 (p 153)

26. See also Ref 22 (p 257) citing The T. J. Hooper, 60 F. 2d 737, 740 (2d Cir. 1932), and Ref 8, §295-A, Comment *c*, Illustration 2; Leonard vs Watsonville Community Hospital, 47 C 2d 509, 519 (1956).

27. UCSF does not have a similar bylaw. The JCAH Accreditation Manual was revised in 1974 to require the pathologist to "participate in the hospital's patient care evaluation program." JCAH Accreditation Manual for Hospitals (1973) 131 as revised to 1975. See *infra* Ref 34.

28. "It is elementary that the knowledge received during the course of their employment as nurses is in legal effect binding upon their employer, the defendant Hospital." Goff vs Doctors General Hospital, 166 CA 2d 314, 316, 319, 1958 (failure of nurse to report she was "horrified" by doctor's treatment)

29. Sheridan B: Why the Lawyers Caught Nork and the Doctors Didn't. Medical Economics, 51:91, 95-96, Jul 22, 1974 (raises the question but does not give the answer). Compare Ref 5 (pp 58-59), 173, 182. Pffs Exh 188.

30. Gonzales vs Mercy Hosp., Tr. October 9, 1973, p 152 line 26-27. See also *id.* 150 lines 25-27

31. Restatement (Second) of Agency §354 (1958); Schwartz vs Helms Bakery Limited, 67 C 2d 232, 238-39, 1967. The medical staff is the agent of the governing body (the hospital), 22 Cal Adm Code §§ 70701 ¶6, 70703 ¶(a), ¶(h) (1975). The staff and the body may both be liable. Corleto vs Shore Memorial Hospital 350 A 2d 534 (NJ Super 1975), Ref 37, Ref 8, §324A

32. Hill vs James Walker Memorial Hospital, 407 F 2d 1036 (4th Cir. 1969). Cf. Betesh vs United States, 400 F. Supp. 238, 246 (D.D.C. 1974) (Maryland law applied).

33. 407 F 2d at 1042. For the same conclusion on other facts see Hill vs United States Fidelity and Guaranty Co., 428 F 2d 112 (5th Cir 1970) (safety engineering inspections) and Donald vs Garry, 19 CA 3d 769, 771, (attorney's lack of diligence).

34. Joint Commission on Accreditation of Hospitals, Accreditation Manual for Hospitals 1970, updated 1973, i.v. 37, 40, 42, 43, 45, 48 (as revised to 1975), *supra* Ref 27. See also the standards on Quality of Professional Services added in March 1975. *Id.* between 22 and 23. Note that on the related but separate problem of staff

appointments and reappointments the evaluation procedure "should be . . . strict enough to safeguard patients." *Id.* 42

35. University of California San Francisco, Bylaws of The Medical Staff 3, 1974

36. Coffee vs McDonnell Douglas Corp., 8 C 3d 551, 557, 1972

37. 138 NJ Super 302, 350 A. 2d 534 (1975)

38. Matchett vs Superior Court, 40 CA 3d 623, 629, 1974, discussion Ev. Code §1157. Previously the court had held that although proceedings before medical society committees relative to settlement of claims under malpractice insurance policies were not discoverable because they were "work products' of the attorneys defending malpractice actions, Brown vs Superior Court, 218 CA 2d 430, 444, 1963, records of similar hospital staff meetings were discoverable, Kenney vs Superior Court, 255 CA 2d 106, 109, 1967. See generally, American Hospital Association, Quality Assurance Program, §10 Motivation for Commitment to the Program (1972) (collecting various statutes).

At least two reported opinions of trial courts suggest that statutes protecting hospitals and doctors may deter rather than promote improvement of the quality of patient care. Corleto vs Shore Memorial Hospital, 138 NJ Super 302, 350 A 2d 534, 539, 1975: "[I]t can be argued that subjecting persons in the class [medical staffs and hospital officials] to liability will serve to make them more aware of their responsibilities in assuring that only competent physicians practice within their hospitals, thereby raising the level of medical care within the State." Graley vs Satayatham, 343 N.E. 2d 833, 838 (Ohio CP 1976): "To the extent that in tort actions of the malpractice type if the medical profession is less accountable than formerly, relaxation of medical standards may occur with the public the victim."

39. Eg, Calif Stats 1975, 2d Ex Sess cc 1 and 2. Statutes of this sort, including limitations on recovery such as those now in Civ. C. §3333.2, are said to be under constitutional attack in several states. One has already been invalidated under the special legislation prohibitions of the Illinois Constitution, Wright vs Central Du Page Hospital Association, 347 N.E. 2d 736, 743 746 (Ill 1976); and a trial court in Ohio has held such a statute unconstitutional under both the Ohio and United States Constitutions, Graley vs Satayatham, 343 N.E. 2d 832, 838, 839 (Ohio CP 1976). In Nork vs Superior Court, 33 CA 3d 997, 1003, 1973, the court noted the possibility of constitutional problems, but had no occasion to resolve them.

40. In Rosner vs Eden Township Hospital District, 58 C 2d 593, 598-99, 1962, the court referred to "vague and ambiguous" hospital rules that might become a means of "arbitrary discrimination" or retaliation for testifying for plaintiffs in malpractice cases, i.e., breaking the "conspiracy of silence" referred to in Salgo vs Leland Stanford etc. Bd. Trustees, 154 CA 2d 560, 568, 1957. The inadequacy of medical licensing procedures is mentioned in Moore vs Board of Trustees of Carson-Tahoe Hosp., 495 P. 2d 605, 608 (Nev 1972)

41. Cousins N: Malpractice—With or without insurance. Saturday Review, Mar 20, 1976, p 4

Proposed CMA Constitutional Amendment for Action in 1978

One Constitutional amendment was introduced in the 1978 California Medical Association House of Delegates. Under the terms of the Constitution, this amendment must lie on the table until the next regular meeting of the CMA House of Delegates.

* * *

Article VIII, Section 3.—Publication of Constitutional Amendments

Introduced by: Council
Representing: Executive Committee
Author: Executive Committee

Constitutional Amendment 1-78
Committee G

RESOLVED: That Article VIII, Section 3.—Amendments of the Constitution of this association be amended by deleting the words in brackets and adding the words in italics, so that it now shall read:

Any member of the House of Delegates at any meeting of any session, other than a special session, thereof may present an amendment or amendments to any article or articles or any section or sections of any article or articles of this Constitution.

Such proposed amendment or amendments shall be in writing and shall be filed with the secretary and shall thereafter be published at least twice in separate issues of [the official journal of this Association] *a member-wide publication of this Association* prior to the next session of the House of Delegates.

At the said next session, other than a special session of the House of Delegates, such proposed amendment or amendments shall be submitted to the House of Delegates, . . .

Refer to: Cabeen WR Jr, Roberts NK, Child JS: Syncope and the sick sinus syndrome (Clinical Notes in Diagnostic Cardiology). West J Med 129:452-455, Nov 1978

Syncope and the Sick Sinus Syndrome

WILLIAM R. CABEEN, JR, MD
NIGEL K. ROBERTS, MD
JOHN S. CHILD, MD
Los Angeles

SYNCOPE can be a troublesome and relatively common patient presentation with a variety of possible causes. Many cases are due to cardiac disease that results in periods of decreased cerebral blood flow. Prominent among the cardiac causes is the so-called sick sinus syndrome, an entity the spectrum and prevalence of which have become progressively more apparent in the past decade.[1]

The diagnosis of sick sinus syndrome includes a number of manifestations or mechanisms of abnormal sinus node function such as spontaneous decrease or failure of sinus automaticity (or both), exaggerated suppression of sinus automaticity by rapid or premature atrial activity and sino-atrial conduction block.[1,2] In addition, carotid sinus hypersensitivity, which may exist independently of intrinsic sinus node disease, may result in sinus node dysfunction due to vagal overactivity or sympathetic underactivity.[2] These mechanisms can appear as sinus bradycardia, sinus arrest, sino-atrial exit block or alternating bradycardia and tachycardia or vice versa, the so-called tachy-brady syndrome. While occasionally the mechanism is apparent on routine electrocardiography, usually it is not, or the abnormality noted (usually sinus bradycardia) is an incomplete expression of the patient's sinus node dysfunction. Therefore, further evaluation is required to understand and manage the patient appropriately.

A case we have recently seen is typical and illustrates the approach to and findings from such a patient. He was a 69-year-old man who presented after the second of two episodes of syncope lasting several seconds. He gave a history of intermittent lightheadedness during the past six months and exertional angina during the past nine years which recently had occurred only after meals followed by exercise. The angina was relieved promptly by nitroglycerin and was not a disabling symptom.

Results of physical examination were normal except for the finding of periods of irregular pulse. An initial resting 12-lead electrocardiogram (ECG) (Figure 1, 8:16 AM) showed atrial fibrillation with a ventricular response rate of 130 beats per minute and prominent ST segment depression. A short time later a repeat ECG showed sinus bradycardia, with a rate of 57 beats per minute, and improved but still abnormal ST-T waves (Figure 1, 10:30 AM).

Because of the history and these findings, additional studies were carried out to investigate a possible cardiac cause of the patient's syncope. A 24-hour Holter tape ECG monitoring study was done. It showed sinus rhythm and periods of atrial flutter and fibrillation during which the patient was asymptomatic. However, when the atrial flutter spontaneously terminated there were long pauses before cardiac rhythm resumed, due to failure of return of sinus rhythm or an appropriate lower escape rhythm (Figure 2). During these pauses the patient felt transient lightheadedness. These findings identified the patient's symptoms as being due to excessive overdrive suppression of his sinus node by atrial tachyarrhythmias and allowed appropriate diagnosis and treatment (see below).

When long-term ECG recording does not show such findings and other causes of syncope have been excluded, patients can be further evaluated by (1) rapid atrial pacing followed by termination and measurement of sinus return time or "sinus node recovery time" and (2) programmed single atrial premature stimuli to evaluate sinus response.

In a similar case—the patient was 65 years old, also with syncope and intermittent atrial flutter—the Holter 24-hour ECG recording showed only sinus bradycardia at a rate of 50 beats per minute. Pacing studies were therefore done. Atrial pacing resulted in atrial flutter which was terminated by rapid overdrive atrial pacing. Following

From the Departments of Medicine and Pediatrics, Division of Cardiology, University of California, Los Angeles, School of Medicine.

Reprint requests to: William R. Cabeen, Jr., MD, Division of Cardiology, Department of Medicine, UCLA School of Medicine, 10833 Le Conte Ave., Los Angeles, CA 90024.

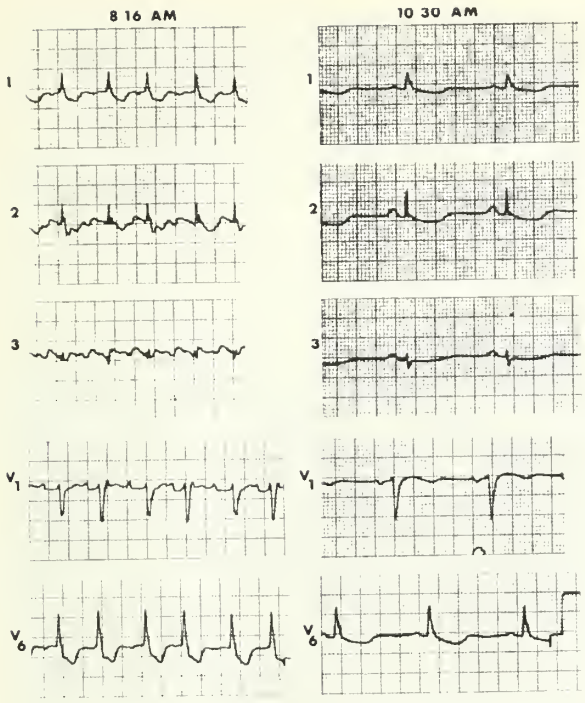

Figure 1.—Left, 8:16 AM. Initial electrocardiogram showing atrial fibrillation and abnormal ST-T waves. **Right,** 10:30 AM. Electrocardiogram approximately two hours later showing return to sinus rhythm.

termination of atrial flutter there was a pause in *atrial* rhythm of 10.5 seconds (Figure 3—note the lack of electrical activity in lead RA). Asystole was prevented by the escape of a temporary ventricular demand pacemaker (VS, Figure 3), followed by a junctional escape rhythm (J, Figure 3). In this second case, atrial pacing techniques showed the same mechanism of sinus dysfunction, namely excessive suppression of sinus automaticity by rapid atrial activity. Absence of an appropriate atrial or junctional escape rhythm also is an abnormality and one which usually must coexist in *symptomatic* patients with sick sinus syndrome.[3] Both of these patients, then, had symptoms due to suppression of sinus automaticity by atrial tachyarrhythmias, flutter and fibrillation. In the first case, this was discovered on a Holter monitor, in the second, pacing techniques were required to show the abnormality. In both patients a permanent pacemaker was implanted. This insured that such pauses in cardiac rhythm could not occur. In addition, antiarrhythmic drugs were given to control the atrial tachyarrhythmias. Theoretically symptoms could be prevented by preventing the tachyarrhythmias with drug ther-

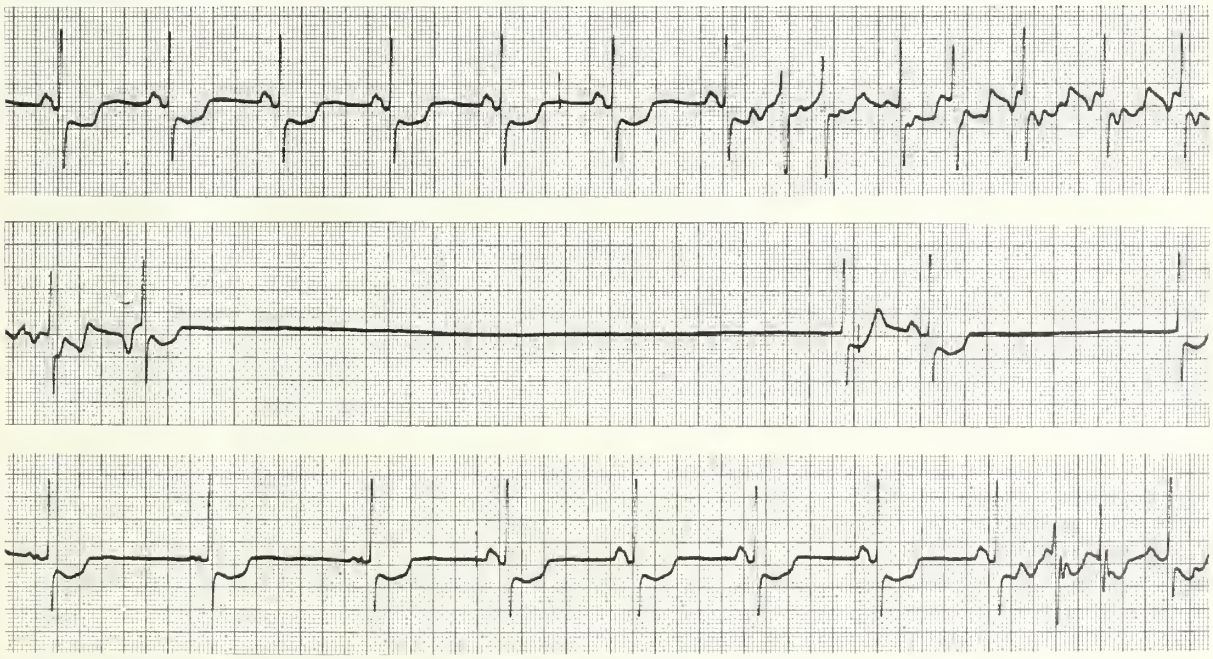

Figure 2.—Holter tape monitor tracing showing sinus rhythm, rate 60, followed by a premature atrial complex initiating a brief episode of atrial fibrillation which provides rapid stimuli to the sinus node. Following spontaneous termination of the atrial fibrillation there is asystole for 6.3 seconds at which time the patient was lightheaded. Asystole is terminated by a junctional escape rhythm. The first junctional escape is followed by a sinus impulse but sinus rhythm does not finally return until after 14 seconds; after a brief period of an atrial escape rhythm. This tracing shows (1) overdrive suppression of sinus automaticity by atrial fibrillation and (2) abnormally slow junctional and atrial escape and lack of ventricular escape, all of which are abnormal and reveal the mechanism of the patient's lightheadedness and syncope.

apy, and therefore sinus suppression would not occur, but the use of drugs may depress escape pacemaker function even more and it is difficult to be confident that the tachyarrhythmias can be totally prevented. The use of a permanent pacemaker therefore protects the patient from excessive pauses in rhythm, should tachyarrhythmia recur.

Discussion

In a patient who presents with syncope, the clinician must be aware that abnormal sinus node function can be the cause and that it may not be manifest on routine physical examination or ECG, whereas most other strictly cardiac causes of syncope (for example, aortic stenosis, primary pulmonary hypertension, iodiopathic hypertrophic subaortic stenosis, left atrial myxoma, congenital prolonged QT syndrome, etc.) do have findings to guide further diagnostic efforts. Therefore, one must remember the possibility of abnormal sinus

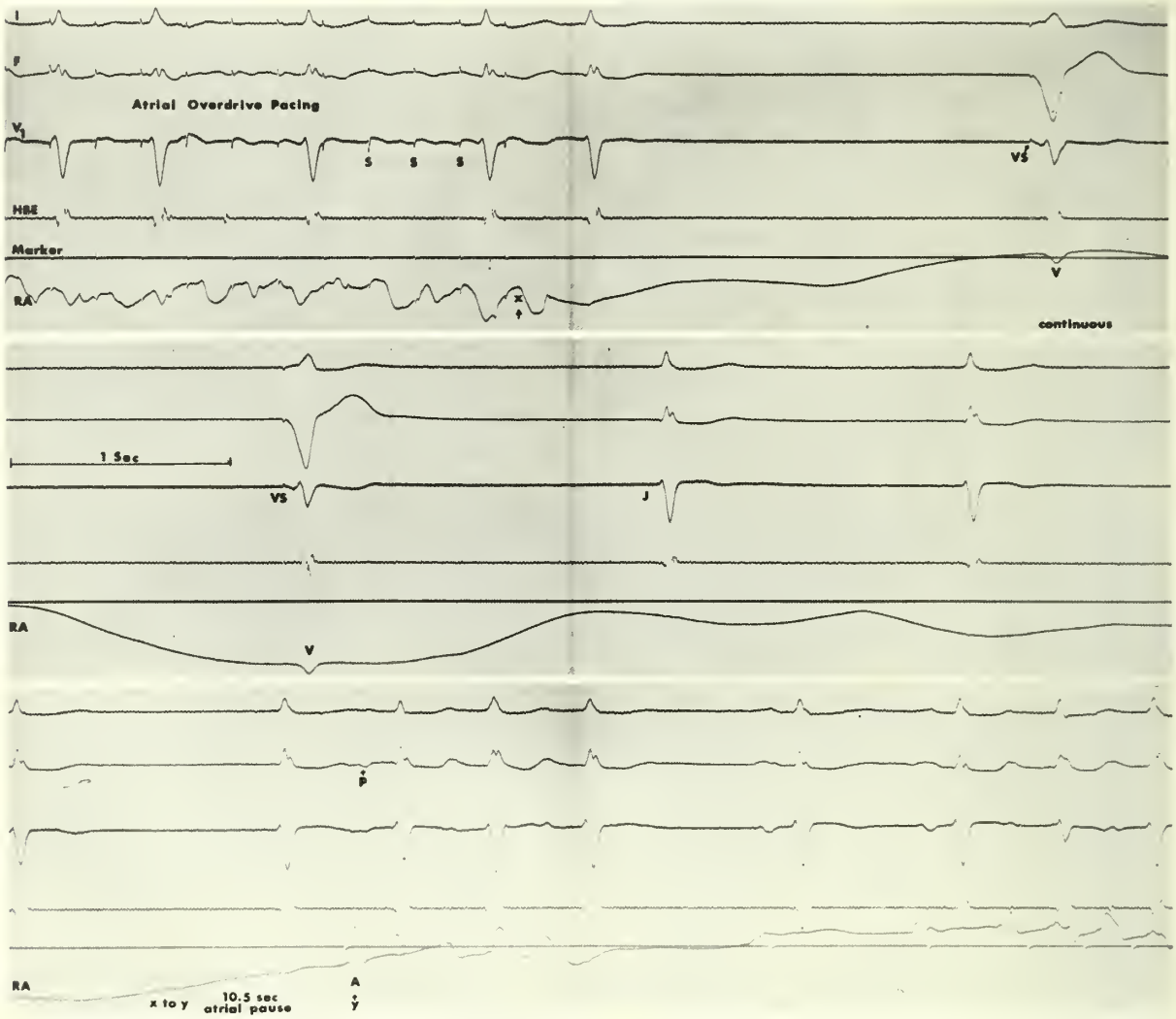

Figure 3.—Atrial pacing study—Atrial flutter has been initiated by atrial pacing (not shown on tracing). Rapid overdrive stimulation, (S, **first panel, left**) when terminated, results in termination of the atrial flutter and reveals failure of return of sinus node activity. Thus, note lack of atrial activity in right atrial lead (RA) for 10.5 seconds from x on the first panel to y on the third panel (deflections seen in lead RA between x and y are ventricular depolarization [V]). Asystole is prevented by escape of a ventricular demand pacemaker (VS) initially, then a junctional escape rhythm (J). This shows (1) abnormal suppression of sinus automaticity by rapid atrial activity and (2) abnormal intrinsic escape pacemaker function. I, F, V_1 are recordings of the corresponding surface electrocardiogram leads, HBE is the electrocardiogram recording in the His bundle position (although the His deflection is not recorded on this tracing), "marker" records a deflection each time the pacemaker used senses or stimulates, RA is the right atrial electrocardiogram recording, S indicates atrial pacemaker stimulus, VS indicates ventricular demand pacemaker stimulus, V indicates ventricular depolarization, J indicates a complex of junctional origin, P indicates spontaneous P wave, A indicates atrial depolarization as seen in RA lead, x and y are reference points indicating last paced and first spontaneous atrial activity respectively. (Paper speed 100 mm/second.)

function (either intrinsic or due to excessive autonomic influence as with carotid sinus hypersensitivity) and search for its presence.

In addition to syncope, suggestive findings are (1) resting sinus bradycardia; (2) pause in sinus rhythm of greater than three seconds with carotid massage;[4] (3) absence of expected heart rate increase in the strain phase of the Valsalva maneuver and of slowing during the post Valsalva blood pressure overshoot;[4] (4) less than expected increase in sinus rate with exercise; (5) minimal rate increase following intravenous administration of 0.6 to 1 mg of atropine (that is, to less than 90 beats per minute),[5] and (6) failure of return of adequate sinus rhythm after conversion (spontaneous or direct current cardioversion) of atrial tachyarrhythmias.

As described, Holter monitoring and, if this is unrevealing, atrial pacing studies can be done to show abnormal sinus function. Holter monitoring, of course, records the spontaneous occurrence of dysfunction. When the patient's presenting symptoms and an abnormal rhythm occur together their cause and effect relationship is shown. The occurrence of symptoms *without* accompanying rhythm abnormalities excludes cardiac rhythm dysfunction and allows evaluation to proceed to other areas.

If Holter monitoring is unhelpful, then, to detect abnormal function, atrial pacing studies are done to stress the sinus node. Normally, when atrial pacing at rates from 100 to 180 beats per minute is terminated, sinus activity will return after 1,200 to 1,400 msec.[1] In many patients with sick sinus syndrome the sinus node recovery time will often be notably prolonged (Figure 4). This may be due either to excessive overdrive suppression of automaticity (Figure 4), or to sino-atrial conduction block of the return sinus impulse.[6] The latter mechanism, sino-atrial block, is less common, but is the likely cause when the apparent sinus node recovery time is an even multiple of the subsequent sinus cycle length or when, after return of spontaneous rhythm, there is a pause in atrial activity equal to a multiple of the basic cycle length.[6] Therefore, in sino-atrial block the first post-pacing cycle may appear appropriate but the subsequent cycles are excessively prolonged.[6,7] In either case, pauses in atrial activity after rapid atrial pacing, either immediately (prolonged sinus node recovery time) or shortly after manifest return of spontaneous activity, are to be taken as evidence of abnormal sinus function and suggest this as a mechanism for syncope.

Conclusion

The occurrence of syncope may be due to abnormalities of cardiac rhythm and the possibility of sinus node dysfunction should be considered in such patients. Clinical clues such as sinus bradycardia, lack of a classic response to the Valsalva maneuver, exercise or administration of atropine strengthen the possibility. Unless the routine ECG shows diagnostic abnormalities evaluation with 24-hour Holter ECG tape monitoring and, if necessary, atrial pacing studies must be done. Once shown, the usual treatment is permanent pacing. Although permanent atrial pacing with a rate adjustable demand pacemaker would seem preferable, the fact that frequently significant atrioventricular (AV) node conduction defects are associated with sick sinus syndrome and difficulties with the stability of permanent atrial pacemaker leads make ventricular demand pacemaking the most acceptable approach at the present time.

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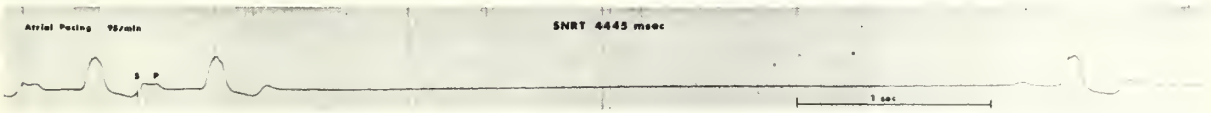

Figure 4.—Example of sinus node recovery time determination (not from cases presented). On the left portion of the figure the atrium is paced at a rate of 95. Following termination of pacing there is a pause in atrial rhythm for 4.4 seconds, the sinus node recovery time. An associated abnormality is the failure of lower escape foci to fire. (Paper speed 100 mm/second.) S indicates atrial pacemaker stimulus, P indicates atrial depolarization or the P wave; SNRT is sinus node recovery time.

Refer to: Spital SE: Understanding physicians' rights and liabilities under the California Medical Practice Act (Information). West J Med 129:457-459, Nov 1978

Information

Understanding Physicians' Rights and Liabilities Under the California Medical Practice Act

SAMUEL E. SPITAL, Esq, *San Diego*

THE RELATIVELY SECURE DOMAIN of the physician in California is being jeopardized by attacks upon his competence. An ever-increasing number of malpractice suits, many culminating in successful claims, as well as disciplinary actions by the state's Board of Medical Quality Assurance (BMQA) are challenging the physician's favored position in society.

In light of this growing problem, physicians no longer can practice medicine as they once did. It is essential that every California physician thoroughly examine all aspects of his practice and familiarize himself with his rights and liabilities under the state's Medical Practice Act and BMQA's enforcement procedures.

The Administrative Process

The purpose of disciplinary proceedings by BMQA is to protect the public from incompetent, dishonest or unprofessional licensees. BMQA, a division of the state's Department of Consumer Affairs, consists of three sections: Division of Medical Quality, Division of Licensing and Division of Allied Health Professions. The Division of Medical Quality utilizes approximately 45 investigators to review complaints against physicians. These complaints arise from anonymous sources, former employees, patients and other physicians. Complaints may also emanate from the division's own investigations, as in the case of any judgment or settlement in excess of $3,000 arising from a lawsuit involving negligence, error or omission in the practice of medicine.

Depending upon the results of the investigation, the matter might be referred by the investigator to the attorney general, a district attorney or a city attorney. A district or city attorney must limit his determination to whether there is any criminal violation. If he files charges against the physician, the penalty can be a fine and/or jail sentence.

The attorney general, on the other hand, determines whether there is cause for disciplinary action. A deputy attorney general analyzes the investigation report and accompanying material to determine whether there is sufficient evidence to warrant filing an "accusation." This is the initial pleading in licensing proceedings.

The accusation must set forth in ordinary, concise language the acts or omissions with which the physician is charged (thereby enabling him to prepare his defense) as well as the statutes and rules which the physician is alleged to have violated. After the accusation is prepared by the deputy, it is sent to BMQA for signature and filing. Usually BMQA's executive director signs the accusation; he is the complainant. After the accusation is returned to the deputy, it is served on the physician by certified mail.

There is no statute of limitations requiring that the accusation be filed within a prescribed period of time. Nevertheless, BMQA must prosecute promptly. If delay prejudices the physician's rights, a motion to dismiss the accusation might be entertained.

A physician receiving an accusation should immediately consult an attorney, preferably one with experience in disciplinary matters before the Division of Medical Quality. It is necessary to file, within 15 days, a "notice of defense" form, which sets forth the physician's request for an administrative hearing. If he fails to file the notice, the matter will proceed by default, and his license almost certainly will be suspended or revoked. On receipt of the physician's notice of defense, the Office of Administrative Hearings will assign an administrative law judge to hear and decide the case. Depending upon the anticipated duration of the hearing, it will begin three to six months after filing of the accusation.

The physician is entitled to know the names, addresses and statements of all witnesses against him. In addition, the physician has the right to

The author, formerly a deputy attorney general, State of California, is now in private practice in San Diego. He is primarily engaged in disciplinary matters involving licensees of State agencies, including the Board of Medical Quality Assurance.

Reprint requests to: Samuel E. Spital, JD, Security Pacific Plaza, Suite 1200, 1200 Third Avenue, San Diego, CA 92101.

obtain copies of all written and other documentation admissible into evidence, as well as investigative reports. This procedure, known as "discovery," must be initiated within 30 days after service of the accusation. If discovery is thwarted, the physician may compel it by filing a petition in superior court.

At the hearing, the deputy attorney general produces oral and documentary evidence to sustain the allegations in the accusation. The physician has the right to cross-examine the witnesses who testify against him. After the complainant rests his case, the physician presents evidence in his favor by testifying himself and by calling witnesses in his behalf. Any relevant evidence is admissible, including hearsay evidence (an out-of-court statement made by someone other than the witness). Although hearsay evidence alone is not sufficient to support a finding by the administrative law judge, it is admissible to supplement or explain other evidence.

After presentation of evidence is completed, the administrative law judge receives oral or written argument from the parties. The administrative law judge then prepares a written "proposed decision." This document, usually several pages long, contains findings of fact, determination of issues and a recommended penalty or disposition of the case.

Even if there are grounds for disciplinary action, there could be circumstances where it would not be in the public interest to impose a penalty (for example, the physician technically violated the law, but there are mitigating or extenuating circumstances). Although it is possible the proceedings could be terminated without a penalty, as by dismissal of the accusation, this type of disposition is disfavored. Penalties can range from a stayed suspension with a minimal conditions of probation to an actual suspension or revocation of medical license.

The Division of Medical Quality may adopt the proposed decision in its entirety or may reduce the penalty without examining the transcript of the hearing. On the other hand, if the division decides to increase the penalty, it must order the hearing transcript from the Office of Administrative Hearings. After the transcript is prepared but before the division issues its decision, each party is afforded another opportunity to present oral or written argument.

In the event the decision is unfavorable, the physician may petition for reconsideration. In this regard, a stay of the decision may be desired to afford the physician sufficient time to prepare his petition or to "put his affairs in order" in the event a suspension or revocation is imposed.

If the petition is denied, the matter can be appealed to superior court. *Judicial* review may be sought by filing a "petition for writ of mandate." It is crucial that this be filed within 30 days after the last day on which reconsideration superior court, the physician must establish that can be ordered. If a stay is sought from the there is no harm to the health and safety of the public and that it is not likely the division will prevail on appeal. This is an onerous burden, which can be lightened considerably with the help of an attorney experienced in these matters.

Grounds for Revocation or Suspension

The various grounds for disciplinary action are set forth in the Medical Practice Act (Business and Professions Code, commencing at Section 2000). The provisions most frequently utilized by the division as the basis for disciplining physicians are aiding or abetting any unlicensed person to practice medicine; the commission of any act involving moral turpitude or dishonesty; conviction of a felony or any offense involving moral turpitude; prescribing without a good-faith prior examination; intoxication-related offenses; gross negligence; and incompetence.

The list of grounds for disciplining is extensive, and each such ground may include a variety of circumstances. However, a physician has a number of potential defenses available to him. He may assert that the patient did not elect to undergo the treatment plan or procedure he recommended; that the unlicensed activity or misconduct which allegedly was performed on his premises was not at his direction, nor did he have knowledge of it; that all alleged deficiencies were corrected prior to the filing of the accusations; or that the patient deliberately fabricated the allegations.

These potential defenses are in addition to any claims of unconstitutionality of the statutes or rules or of violation of due process or other rights guaranteed to the physician by the Constitution. Evidence in mitigation or evidence tending to show rehabilitation are crucial in disciplinary matters.

When a physician's competence is at issue, he is

1. *History*—Is a complete history taken of each new patient? Is it frequently updated?
2. *Treatment*—Has a straightforward and honest appraisal of the patient's condition been presented to him? What treatment is indicated? What tests are or may be required? Should the patient be referred to a specialist? Are all alternatives carefully explained? Are all of the uncertainties and potential complications fully described? Is an experimental procedure being utilized? Are sufficient records maintained?
3. *Drugs*—Is the prescription clear? Is the patient advised of possible undesirable effects? Is a duplicate copy stapled to the patient's chart or is a separate one-page medication record maintained as in the case of hospital charts? Are his allergies and other past reactions to treatments or drugs carefully noted?
4. *Informed consent*—The treatment plan or medical procedure should be set forth and documented. If practical, it should be signed by the patient several days before treatment is started. A physician should inform his patient of what he is going to do and of possible complications that might result from his treatment or procedure. This is known as informed consent. It is important that a physician *document* that he has provided the following information to the patient: (1) a statement of what kind of operation or treatment is to be carried out; (2) what kind of anesthesia will be used, if any; (3) what side effects and minor discomforts are associated with such operation or treatment; (4) what are some of the serious health problems or complications; (5) whether the procedure is irreversible: (6) what are the alternatives, if any. There must be some *documentation* of the factual statements of the discussion between physician and patient. A mere statement that the "risks, complications and alternatives were explained" is insufficient because these are conclusions; the underlying facts must be recorded.
5. *Personnel*—Are the duties and responsibilities of each employee clearly identified and, if possible, written down in an employee "handbook"? Is there an employment contract that embodies these duties? Does each employee know the limits of his responsibility? If an employee is licensed, a copy of his certificate should be placed in the personnel file.
6. *Medi-Cal (Medicaid)*—Who prepares and completes Medi-Cal program claims forms? What checks and balances have been established? Who signs these forms? Are the responsible employees familiar with current regulations?
7. *Laws*—Every California physician should have a current copy of the state's Medical Practice Act (issued by BMQA), and it should be reviewed from time to time. Medi-Cal laws and regulations should be examined and understood; these can be obtained from the California Department of Health Services.

Figure 1.—Checklist for Medical Practices

well advised to establish an abundance of expert evidence supporting his treatment plan or procedures. A physician is not expected to be a guarantor of successful results, nor is he required to possess a perfect knowledge of medical principles. A physician will not be held responsible for following courses of action that subsequently prove erroneous, provided he has not deviated from commonly accepted procedures. However, to be right is not enough; the physician must present a vigorous defense, if he is to protect his license.

While there is no substitute for individual legal counseling, a checklist (Figure 1) is offered as an aid in evaluating the legal implications of various elements of medical practice. These areas and many others should be the subject of continued scrutiny.

BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

QUESTIONS AND ANSWERS ABOUT ACNE—John R. T. Reeves, MD, Assistant Clinical Professor of Dermatology, University of California, San Francisco; Assistant Chief of Dermatology, San Francisco General Hospital. Prentice-Hall, Inc., Englewood Cliffs, NJ (07632), 1977. 111 pages, $5.95.

Written for lay persons, this book discusses acne in exhaustive detail. This is accomplished through a clearly written question-and-answer format. The book is divided into sections concerning pathogenesis and treatment of acne, and also discusses selection of doctors and pharmacies. There is a complete glossary and index.

In the sections on pathogenesis, relevant medical knowledge is reviewed in an understandable manner. Lay misconceptions are discussed and dealt with persuasively. Cosmetics are listed that purportedly do and do not plug pores.

The treatment section covers all systemic and topical medications, as well as office procedures for treating patients with acne. Medications are listed by brand and generic names, with average 1977 prices given. Side effects of the medications and procedures are covered briefly but completely. A short final section summarizes treatment recommendations for various types and grades of acne.

This reviewer is enthusiastic about this type do-it-yourself educational approach for patients. After physicians (particularly general practitioners, pediatricians and dermatologists) read it, they can decide whether to make the book available in their offices. Many patients will read it through their schools. You may find an advanced reading will help in your relationship with patients having acne.

HOWARD I. MAIBACH, MD
Professor of Dermatology
University of California, San Francisco
San Francisco

* * *

HANDBOOK OF PEDIATRICS—Twelfth Edition—Henry K. Silver, MD, Professor of Pediatrics; C. Henry Kempe, MD, Professor of Pediatrics and Microbiology, University of Colorado School of Medicine, Denver; and Henry B. Bruyn, MD, Clinical Professor of Medicine and Pediatrics, University of California, San Francisco; Director of Child Health and Disability Prevention, City and County of San Francisco. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1977, 721 pages, $9.00

The fact that this handbook is now in its 12th edition offers ample testimony of its usefulness to medical students and physicians in pediatric training, and to practicing physicians as well. Each edition has been carefully reviewed and updated, and the authors have succeeded in retaining an emphasis on the clinical aspects of these subjects covered and have included appropriate background information and new developments in the field. Although the size of the volume limits both the extent and depth of coverage, the convenience of its small size is one of its major advantages. It can and should be read during the first week of pediatric training.

The book itself is divided into 32 chapters covering topics such as the pediatric history and physical examination, the management of children during illness, landmarks of growth and development, and the like. Chapters also include emotional problems, adolescence, the various systems of the body and major disease categories. The appendix includes topics such as drug therapy, dosage information, and various normal and abnormal values. The checklist for pediatric screening procedures is particularly useful. Several tables are included which provide summaries of causes, diagnosis and therapy, thereby summarizing information for the benefit of clinicians. A complete and accurate index adds to the value of this manual.

This useful volume should be in the office of each physician who cares for children, and can be recommended to each student of medicine.

PAUL F. WEHRLE, MD
Department of Health Services
Los Angeles County-USC Medical Center
Pediatric Pavilion
Los Angeles

* * *

EMERGENCIES IN MEDICAL PRACTICE—Tenth Edition—Edited by C. Allan Birch, MD, FRCP, Honorary Consulting Physician, Chase Farm Hospital, Enfield, Middlesex. Churchill Livingstone—Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1976. 864 pages, $38.00.

Comprehensive reference textbooks have been published in most medical specialties. In the field of internal medicine, two works—one edited by Harrison and the other by Beeson and McDermott—have achieved the status of definitive reference texts through years of use by internists and frequent revisions reflecting new knowledge and updated standards of medical practice. In emergency medicine, which has only recently developed as a specialty, a comparable reference text has not yet emerged, although at least two comprehensive works have been scheduled for publication in the United States during 1978.

The tenth edition of Dr. Birch's textbook does not meet the needs of a physician working in an emergency department in the United States. The book does not contain a separate chapter on traumatic emergencies. The chapter on medicolegal emergencies is irrelevant to the American experience. A condition which is seen quite commonly here, sickle cell crisis, is cursorily treated in a few short paragraphs. Drug names are generally unfamiliar and some (for example, heroin) are not even available to physicians here. The appendices contain lists of addresses and telephone numbers of facilities supplying services as diverse as hyperbaric oxygen, anthrax information, immunoglobulins and foreign language translation; but the vast majority of these are in Great Britain.

Some of the chapters, such as those on emergencies at sea and emergencies in the air and the section on techniques of embalming, may be relevant to physicians in certain isolated clinical situations. The sections on procedures tend to be rather simplistic (for example, technique of venipuncture) but a few (such as technique of cisternal puncture and of stellate ganglion block) are beyond the scope of usual American emergency medical practice.

Emergencies in Medical Practice has survived ten editions in Great Britain but it cannot serve as a useful reference text for physicians confronted with emergencies in the United States.

JOHN E. CONTE, JR, MD
Associate Professor of Medicine
Chief, Division of Emergency Medicine

WILLIAM F. OWEN, JR, MD
Clinical Instructor of Medicine
Division of Emergency Medicine
Emergency Medicine Fellowship Coordinator
University of California, San Francisco
San Francisco

in memoriam

Allen, Raplh W., Tracy. Died August 22, 1978, aged 42. Graduate of Loma Linda University School of Medicine, Loma Linda-Los Angeles, 1965. Licensed in California in 1966. Dr. Allen was a member of the San Joaquin County Medical Society.

Armanini, George B., Sunnyvale. Died August 20, 1978 at Stanford University Medical Center of heart disease, aged 69. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1937. Licensed in California in 1937. Dr. Armanini was a member of the Santa Clara County Medical Society.

Belford, William W., San Diego. Died September 18, 1978 of heart disease, aged 81. Graduate of the Johns Hopkins University School of Medicine, Baltimore, 1922. Licensed in California in 1925. Dr. Belford was a retired member of the San Diego County Medical Society.

Brown, Cabot, San Francisco. Died September 17, 1978 in San Francisco, aged 76. Graduate of Harvard Medical School, Boston, 1926. Licensed in California in 1926. Dr. Brown was a retired member of the San Francisco Medical Society.

Enright, R. John, Placerville. Died August 29, 1978 of injuries received in a plane crash near Ketchikan, Alaska, aged 43. Graduate of Creighton University School of Medicine, Omaha 1962. Licensed in California in 1963. Dr. Enright was a member of the Sacramento County Medical Society.

Floripe, Felipe O., Long Beach. Died September 5, 1978 in Long Beach of adenosarcoma, aged 64. Graduate of Universidad de Nicaragua Facultades de Medicina en Léon y en Granada, 1940. Licensed in California in 1959. Dr. Floripe was a member of the Los Angeles County Medical Association.

Herrmann, Carrol A., Chino. Died September 2, 1978, aged 68. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1934. Licensed in California in 1934. Dr. Herrmann was a retired member of the San Bernardino County Medical Society.

Hollander, Frederick G., San Diego. Died August 26, 1978 in San Diego, aged 67. Graduate of Loyola University School of Medicine, Chicago, 1937. Licensed in California in 1937. Dr. Hollander was a member of the San Diego County Medical Society.

Impey, Charles C., Castro Valley. Died August 17, 1978 of subdural hematoma and pneumonia, aged 64. Graduate of the University of Nebraska College of Medicine, Omaha, 1938. Licensed in California in 1939. Dr. Impey was a retired member of the Alameda-Contra Costa Medical Association.

Lewis, Karl, Beverly Hills. Died May 31, 1978 in Los Angeles of cancer, aged 87. Graduate of Rush Medical College, Chicago, 1915. Licensed in California in 1920. Dr. Lewis was a member of the Los Angeles County Medical Association.

Marsden, Charles S., jr., San Diego. Died May 15, 1978 in San Diego, aged 68. Graduate of the University of Michigan Medical School, Ann Arbor 1937. Licensed in California in 1937. Dr. Marsden was a retired member of the San Diego County Medical Society.

Meads, Albert Manson, Oakland. Died August 12, 1978 in Oakland, aged 96. Graduate of University of California Medical School, Berkeley-San Francisco, 1908. Licensed in California in 1908. Dr. Meads was a retired member of the Alameda-Contra Costa Medical Association.

Parker, Fenton B., Oakland. Died August 18, 1978, aged 81. Graduate of the University of Oregon Medical School, Portland, 1929. Licensed in California in 1930. Dr. Parker was a retired member of the Alameda-Contra Costa Medical Association.

Schaupp, Karl L., jr., Napa. Died August 29, 1978 in Napa, aged 62. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1942. Licensed in California in 1942. Dr. Schaupp was a member of the Napa County Medical Society.

Swartz, Rex Forest, Long Beach. Died July 15, 1978 of cardiac arrest, aged 85. Graduate of the College of Physicians and Surgeons, Los Angeles, 1918. Licensed in California in 1944. Dr. Swartz was a retired member of the Los Angeles County Medical Association.

Taylor, Pleasant A., San Francisco. Died September 8, 1978, aged 88. Graduate of Tulane University School of Medicine, New Orleans, 1916. Licensed in California in 1917. Dr. Taylor was a retired member of the San Francisco Medical Society.

Terry, Henry M., San Diego. Died August 27, 1978, aged 57. Graduate of the University of Southern California School of Medicine, Los Angeles, 1952. Licensed in California in 1952. Dr. Terry was a member of the San Diego County Medical Society.

Vogelman, Jack G., San Jose. Died September 4, 1978, aged 77. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1935. Licensed in California in 1935. Dr. Vogelman was a retired member of the Santa Clara County Medical Society.

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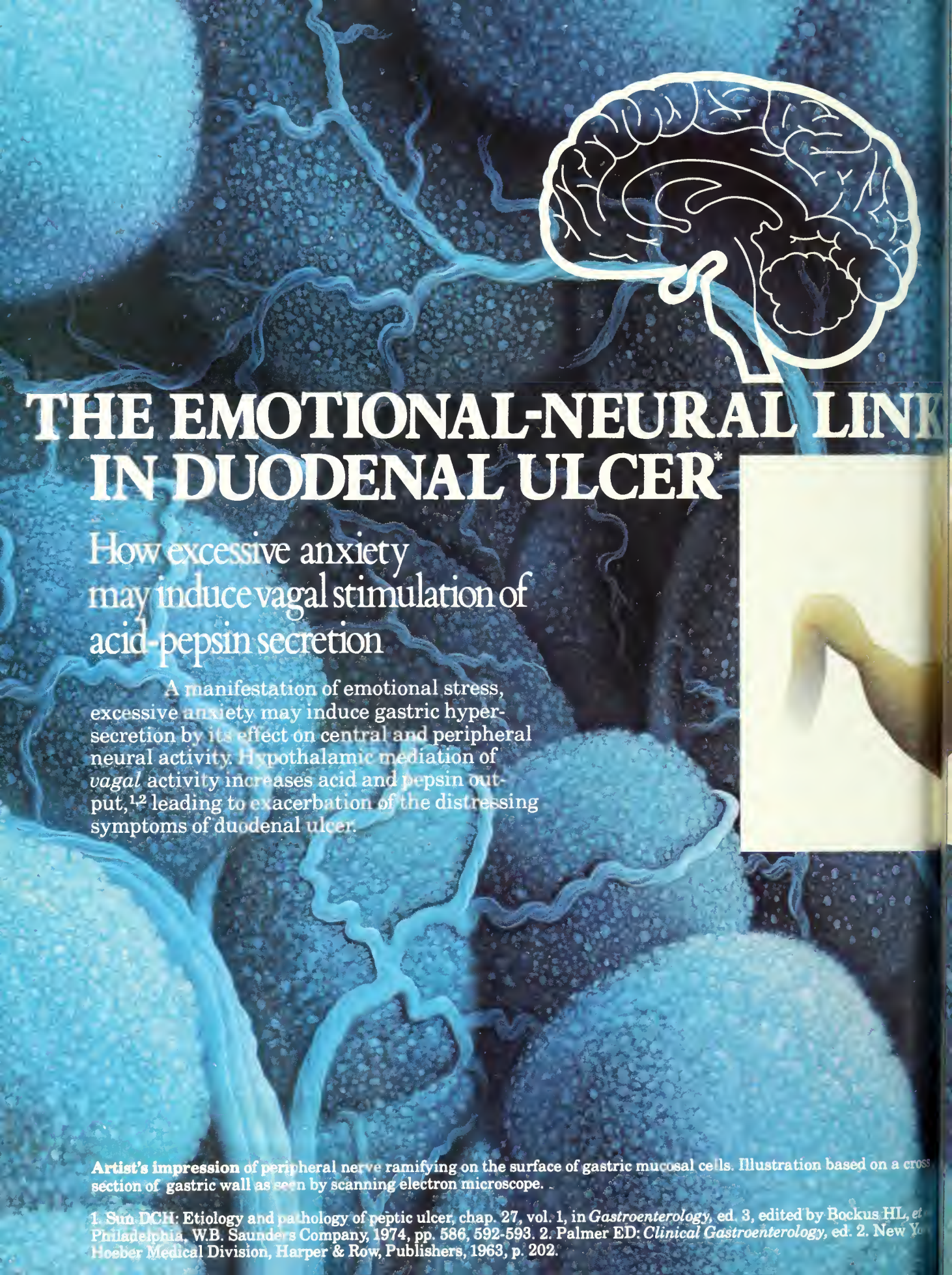

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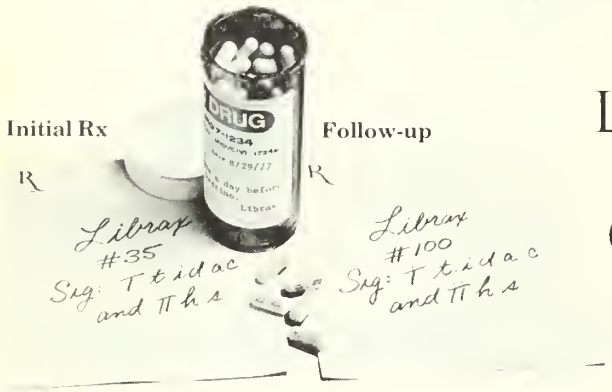

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"Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma, prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.

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As with all anticholinergics, inhibition of lactation may occur.

Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established.

Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, *i.e.*, dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.

Dosage: Individualize for maximum benefit. Usual maintenance dose is 1-2 capsules, 3-4 times/day, before meals and at bedtime. Geriatric patients—see Precautions.

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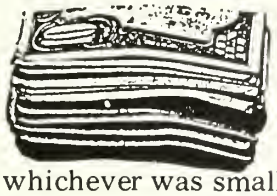

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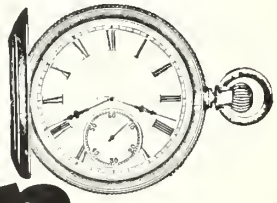

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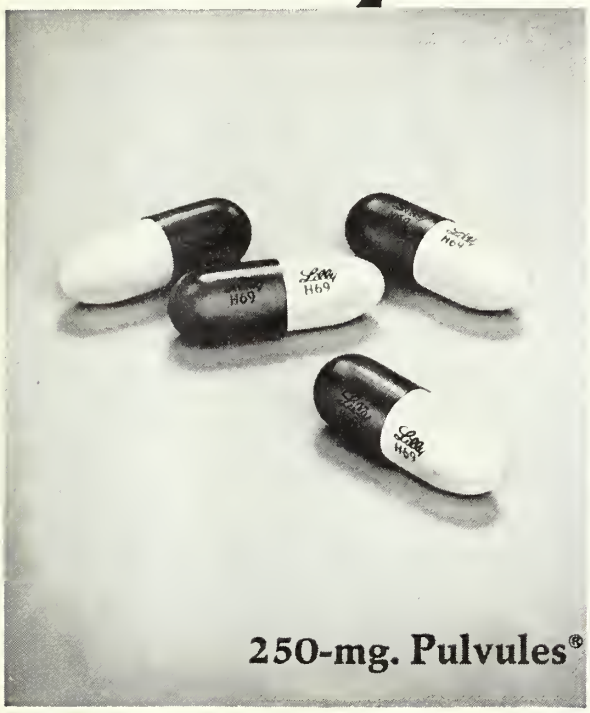

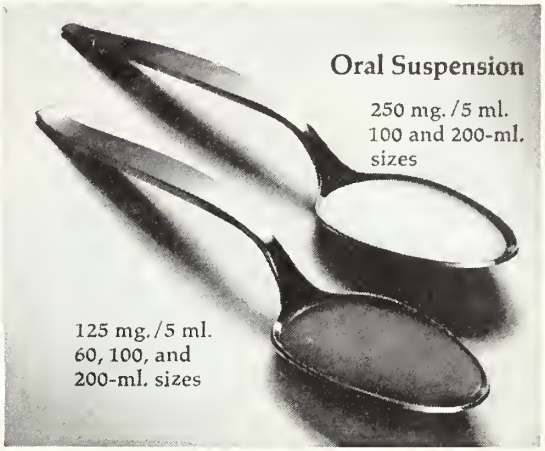

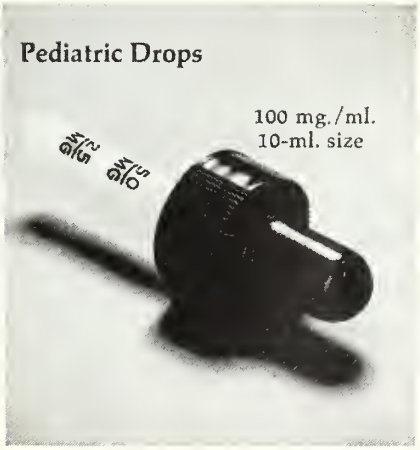

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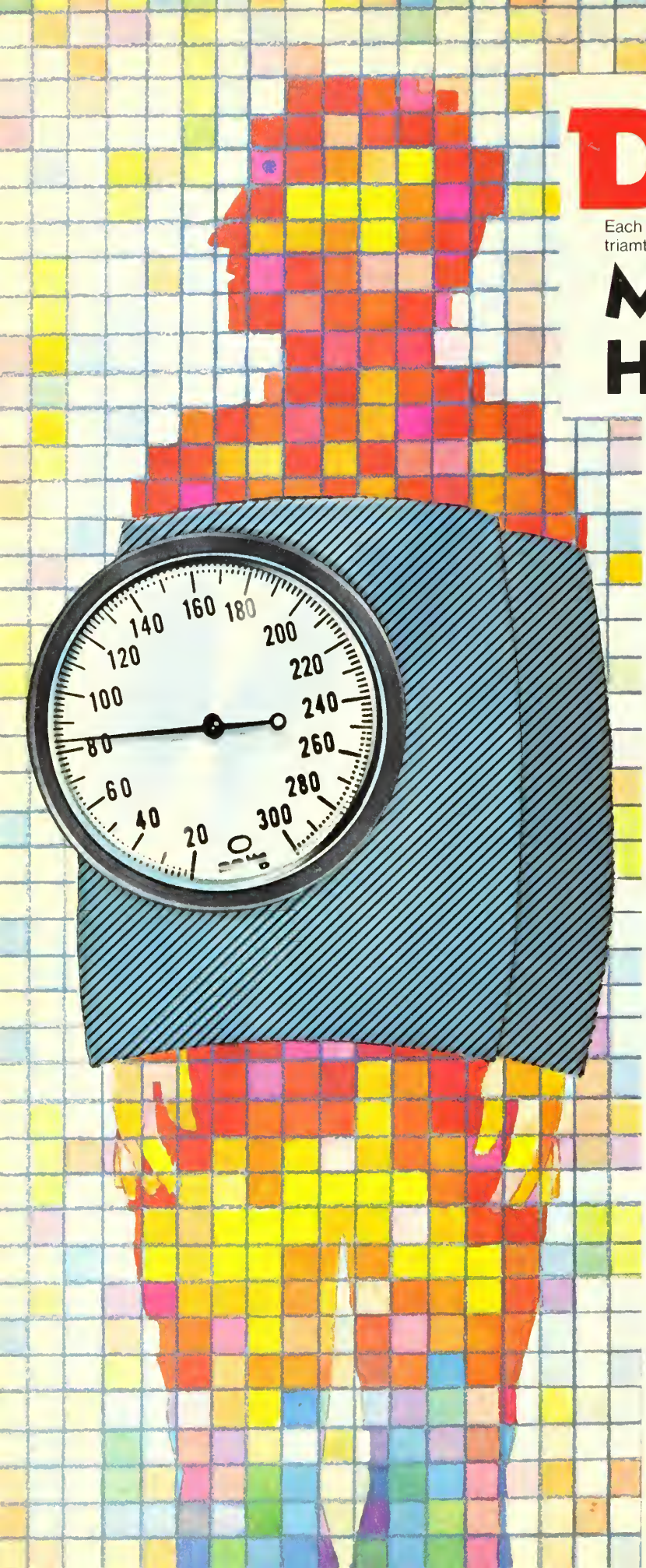

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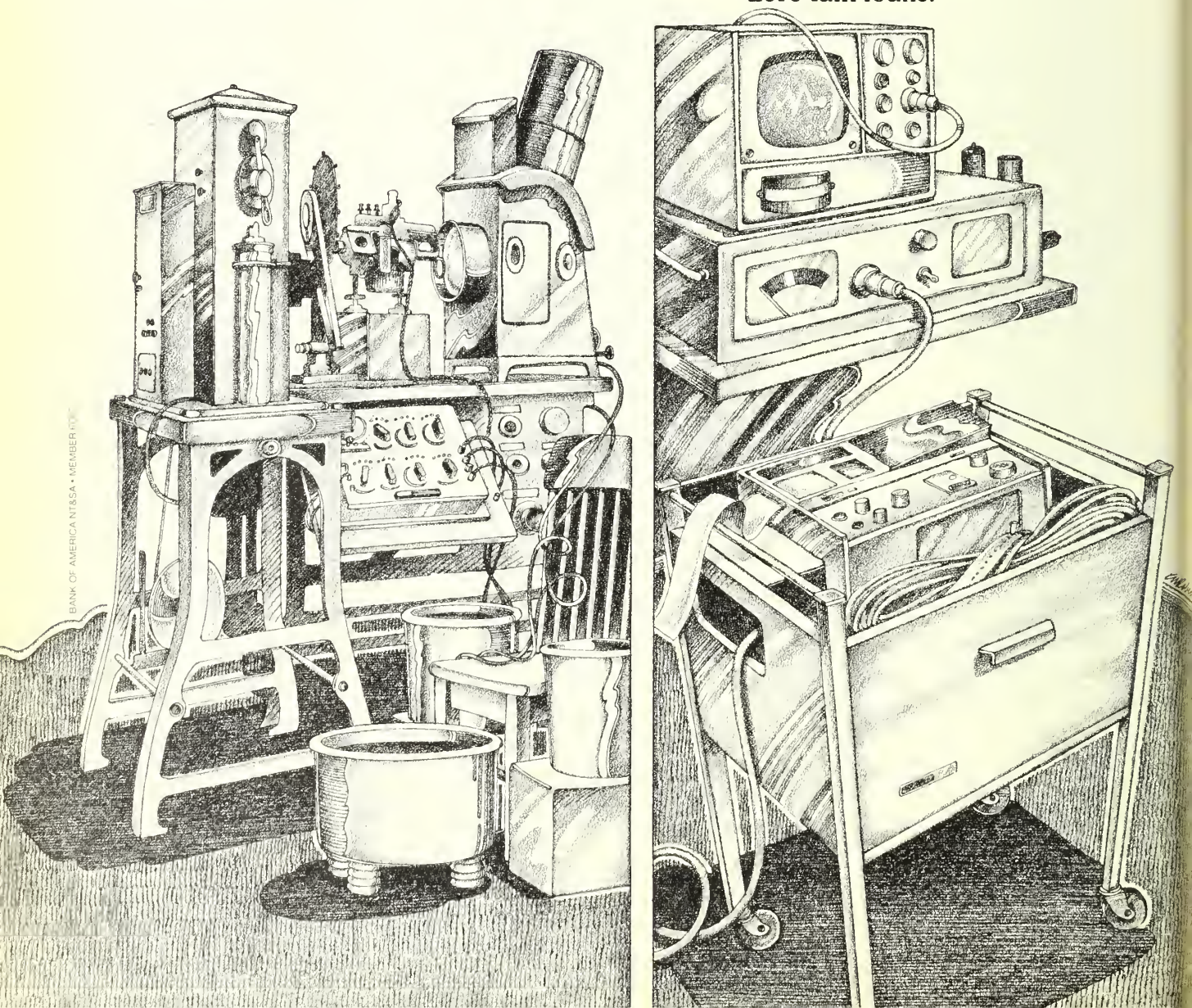

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Refer to: Gray DR, Leaverton DR: Physical child abuse—A review of all cases seen at Sacramento Medical Center in 1975. West J Med 129:461-464, Dec 1978

Physical Child Abuse

A Review of All Cases Seen at Sacramento Medical Center in 1975

DON R. GRAY, MD, *Sacramento, California, and* DAVID R. LEAVERTON, MD, *Albany, New York*

This report presents physical, socioeconomic, demographic and follow-up information on all 18 cases of physical child abuse seen at the Sacramento Medical Center in 1975. Of the 18 abused children, 16 were initially discharged to Children's Protective Service; 13 were placed in foster homes. There were 17 alleged abusers; all were arrested; 12 came to trial; 8 were convicted. Preventive programs offer a less expensive approach and deserve the highest priority.

DESPITE INCREASED public and professional awareness of the phenomenon of child abuse (and a resulting increase in numbers of cases reported),[1] there have been few efforts to assemble detailed quantitative documentation of trends in such specifics as type, extent and treatment cost of injuries; socioeconomic background of parents; judicial actions, and follow-up after release from hospital.[2]

This study was designed to provide data in these areas from the population served by the University of California, Davis/Sacramento Medical Center (UCD/SMC) in 1975. The purposes were (1) to enhance the validity of assessments of the current need for intervention in the Sacramento area by the Suspected Child Abuse and Neglect (SCAN) committee established at UCD/SMC in 1976 and (2) to provide a base for future research that might determine changes in local patterns of child abuse and degrees of success of intervention and prevention strategies.

At the time this paper was submitted for publication, Dr. Gray was a senior medical student at the University of California, Davis, School of Medicine, and Dr. Leaverton was Associate Professor of Psychiatry and Pediatrics, University of California, Davis, Division of Mental Health, Sacramento.

This research was partially supported by NIMH Grant No. MH11864 Undergraduate Training in Medical Education.

Submitted April 4, 1978.

Reprint requests to: David R. Leaverton, MD, Capitol District Psychiatric Center, Albany Medical College, 75 New Scotland Ave., Albany, NY 12208.

The present report is limited to physical abuse involving the individual child and family (level I abuse as defined by Gil).[3] The decision to exclude institutional (level II) and societal (level III) abuse as well as nonphysical (emotional only) level I abuse is a measure not of the importance of these categories but of the greater difficulties of documentation.

Physicians in private practice have been said to be reluctant to report child abuse and even more reluctant to testify about it.[4] This attitude might be understandable if reporting were ultimately ineffective in terms of outcomes for the abused children. While this study could not determine the quality of life for the physically abused children reported, it does document their whereabouts in the period (up to 32 months) following hospital treatment. Children who suffered only emotional abuse and other types of neglect are not reported.

Method

Physical, socioeconomic and demographic follow-up information on 18 physically abused children and 17 alleged abusers was obtained through careful review of hospital, social service and juvenile court records. Additional data regarding the outcomes for the alleged abusers in criminal

ABBREVIATIONS USED IN TEXT

CPS=Children's Protective Service
SCAN=Suspected Child Abuse and Neglect
UCD/SMC=University of California, Davis/Sacramento Medical Center

TABLE 1.—*Types of Injuries Found in 18 Abused Children**

Old traumas (on x-ray studies)	3
Old traumas (other signs)	11
Bruises	16
Hot-water burns	4
Cigarette burns	2
Scratches	2
Fractures	2
Failure to thrive	1

*Some children had multiple injuries.

court were obtained with the cooperation of law enforcement agencies and the district attorney's office. Previous abuse information was obtained through the state Central Child Abuse File. Follow-up data were obtained 20 to 32 months after hospital admission.

Results

Of the 909 admissions to the pediatric service of UCD/SMC during 1975, a total of 44 children were considered possible victims of physical abuse. In 18 cases, suspicions were confirmed by subsequent Children's Protective Service (CPS) and Pediatric Social Service investigation. In the other 26 cases, these agencies found that there was insufficient evidence to justify further investigations.

These children ranged in age from 2 to 102 months; 16 were less than 5 years of age. There were 11 boys and 7 girls. The racial distribution consisted of 12 Caucasians, 3 blacks, and 3 Mexican-Americans. Admissions were distributed almost equally throughout the year without seasonal clustering. The 15 households involved consisted of three married couples and 12 single parents. Twelve families were on welfare, and annual incomes of the remaining three families averaged $9,040.

Table 1 shows breakdown of injuries; children often had more than one injury. Roentgenographic surveys for old skeletal traumas were done in all cases, with positive findings for three of the children. Other signs of old physical traumas were present in 11. The specific types of injuries were as follows: bruises, burns, hot-water burns, cigarette burns, scratches (including abrasions) and fractures. Diagnosis for one child was failure to thrive secondary to neglect. Injuries of two children were considered potentially life-threatening: one skull fracture and one third-degree burn covering 25 percent of the body surface area, for which long-term physical sequelae were scars and contractures that required multiple plastic surgery procedures. There were records of previous abuse for five of the children. There were no deaths during the follow-up period. No sexual abuse was identified in this group.

TABLE 2.—*Disposition of 18 Children Identified as Victims of Physical Abuse*

	Number of Children
Disposition at discharge from hospital	
Home to abusive parent with CPS supervision	1
Home to nonabusive parent	2
Receiving home (CPS)	15
Results of juvenile court hearing	
Declared dependent of court	15
Placed in foster home	13
Placed with nonabuse relative	1
Returned to abusive parent with court supervision	1
Overall status as of December 31, 1977	
Remain in foster home	5
Returned to nonabusive parent	8
Returned to abusive parent with supervision	5

Hospital costs averaged $2,079 per child, with a range from $192 to $21,150. Total hospital costs for the 18 cases amounted to $37,427.

Table 2 indicates the disposition of the children after hospital treatment. As of December 31, 1977, five of the children were still in foster homes; eight had been returned to nonabusive parents; five were with abusive parents, under court supervision.

Of the 18 children admitted to the hospital, 16 were discharged to the custody of Children's Protective Service to await disposition hearings. One child who had been abused by the mother's boyfriend was discharged to the nonabusive mother since the boyfriend had been arrested and charged. The remaining child was discharged home to an abusive mother under supervision of CPS. This family was well known to juvenile authorities. In a review of CPS records in this case, no record of this particular referral was found; however, previous child abuse was noted. This family has subsequently been lost to follow-up.

Of the 16 children discharged to CPS, one was

TABLE 3.—*Outcome in Criminal Procedures for 17 Alleged Abusers*

	Felony Charges	Misdemeanor Charges	Total
Number of arrests	6	11	17
Criminal charges dropped	3	2	5
Criminal charges reduced	2	0	2
Trial verdict: acquittal	0	4	4
Trial verdict: guilty	1	7	8

held for two weeks, then returned to the nonabusive mother after the stepfather had been arrested and she had filed for divorce. The remaining 15 had disposition hearings in juvenile court and were declared dependents of the court. The same judge presided at all these hearings. Thirteen of these court dependents were placed in foster homes; one was placed with an aunt for a period of two months, then placed in the custody of the nonabusive father; and one was returned to an abusive mother under court supervision and with the condition that she receive counseling.

Of the 13 children originally placed in foster homes, five remained with foster parents, with an average stay of 886 days (range from 734 to 940 days) as of December 31, 1977. By the end of 1977 an additional five of the 13 had been returned to the custody of nonabusive parents; the other three had been returned to the abusive parents. Two of these three abusive parents were placed under court supervision, with mandatory counseling. The other child was returned to his natural mother in Mexico (who had sold him for $1,500 to a visiting tourist), at the demand of the Mexican consulate and after lengthy court dispute. The child had come to the United States as an infant. He spoke only English and had developed a warm, nurturing relationship with his foster parents, who wanted very much to adopt him. It is doubtful that the best interest of this boy was a major consideration of the Mexican government. The eight children who were returned to their families after foster care had spent an average of 305 days (range from 90 to 624 days) in foster homes. The quality of these placements, although an extremely important variable in the prognosis, was not assessed.

Seventeen alleged abusers were identified. Their average age was 23.6 years (range from 15 to 38 years), with 65 percent under age 25. The sex distribution was eight men and nine women. Educational level was obtained for 12 of the 17; the average was 10.6 years. Files of CPS revealed that histories of 10 of 13 adults questioned showed that they themselves had been physically abused as children. Of the alleged abusers, 88 percent were unemployed at the time of the abusive incident.

TABLE 4.—*Outcomes for Eight Convicted Child Abusers*

Abuser and Charge	Probation (Years)	Time Served: County Jail (Days)	Time Served: State Prison	Court-ordered Psychotherapy
1—Misdemeanor	3	3	..	x
2—Misdemeanor	3	135	..	x
3—Misdemeanor	3	135	..	x
4—Misdemeanor	3	30	..	..
5—Misdemeanor	5	..	..	x
6—Misdemeanor	..	..	..	x
7—Misdemeanor	..	45	..	x
8—Felony	..	..	*	..

*By March 1978 the father who was convicted of felony child abuse had served 36 months in state prison.

Relationships of the 17 abusers to the children were as follows: mother, seven; father, three; mother's boyfriend, three; father's girlfriend, one; stepfather, two. There was one adoptive mother who had purchased a child in Mexico for $1,500. Of the 17 abusers, 5 were married and 12 were single.

All 17 alleged abusers were arrested. Outcomes of criminal procedures are given in Tables 3 and 4. Eleven were charged with misdemeanors and six with felony child abuse. Subsequently, charges were dropped in five cases and reduced in two. Twelve of those originally arrested came to trial. The one father under felony charges was convicted and was sentenced to serve time in a state prison. Seven were found guilty of misdemeanor child abuse and were sentenced to various combinations of probation, time in the county jail and psychotherapy. Four were acquitted because of insufficient evidence.

Fourteen of the 17 arrests were appropriately reported to the state Central Child Abuse File by the referral agency. Five of those arrested were found to have previous records of child abuse.

Discussion

This report indicates that physical child abuse is common and expensive and that outcomes are varied. Contrary to persistent rumors in the medical community, most of these children were not back in their original homes where the abuse occurred within a few months.

Of the 44 children suspected to be victims of

physical abuse, medical records showed that only 18 were reported to CPS. It seems likely that more were reported but were not documented in the charts. The cross-checking of records indicated many gaps, as is illustrated by the lack of complete reporting to the state Central Child Abuse File.

It is distressing that so many children had to be removed from their families for such long periods. This community (the Sacramento area) has available above-average quality and quantity of mental health professionals. Better communication and coordination among courts, agencies, and support facilities perhaps could have decreased these family disruptions. Should the priorities of these authorities become more oriented to treatment and prevention, children will be returned sooner to stabilized situations.

Failure to identify a case of child abuse can result in very real tragedy. One of our primary goals at UCD/SMC is to develop a keen awareness among housestaff of the problem and to develop a fail-safe system for referral and follow-up of these children.

In the follow-up reported here, most of the children were young, and perhaps for this reason remedial treatment was not given a high priority. There remains some doubt about alleviation of the long-term emotional scars and whether the pattern of attempting to solve problems through violence can be reversed. Successful psychotherapeutic treatment of abused children and their families is now more commonly reported in the literature.[5,6]

Racial distribution, income average and mental status of the persons involved in this study reflect the UCD/SMC service population. Authorities of CPS state that this center is the main referral site for child abuse and thus we would suggest that incidents of abuse in the higher-income families are not adequately reported in this area. Protection for the abused children does not seem to have been a primary concern in the cases reported here, since all suspected abusers were arrested while other child-abuse procedures, such as adequate psychosocial workup and review, were not uniformly carried out. That more cases of older children were not reported may indicate a low level of awareness in those who refer and report. Comparing this report with future data should show trends in types of abuse reported, demographic data about the abusers, the children's age and sex, permanence of injuries, expense involved and degree of previous abuse. Such comparisons can serve as an audit of the evaluations of the SCAN team.

Child abuse can be prevented.[7] As this community institutes programs for prevention and early intervention, future studies should reflect these changes. In view of the tremendous expense and inherent difficulty in comprehensive treatment programs, it is our opinion that prevention programs should have the highest priority.

Summary

Cases of all physically abused children who were admitted in 1975 to UCD/SMC were reviewed. Data concerning outcome for the abused and the abusers are given, thus establishing a baseline to measure changes in incidence, treatment and prevention.

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Refer to: Reuler JB: Herpes zoster. West J Med 129:465-468, Dec 1978

Herpes Zoster

JAMES B. REULER, MD, *Portland, Oregon*

Herpes zoster is a disorder frequently encountered in adults. The natural history is often poorly appreciated and management is frustrating. Recent studies have critically evaluated newer therapeutic modalities. The epidemiology, clinical manifestations, complications and therapeutic alternatives of herpes zoster deserve review.

HERPES ZOSTER is a disorder frequently seen by clinicians caring for adult patients. Its natural course and complications are often very bothersome to patients and the treatment is equally frustrating for physicians. This brief communication outlines the epidemiology, clinical manifestations, complications and therapeutic alternatives of herpes zoster.

Epidemiology

Herpesvirus varicellae is a DNA virus that belongs in the same group as herpes simplex, cytomegalovirus and Epstein-Barr virus. Varicella, or chickenpox, represents primary infection with this agent in the nonimmune host. In greater than 60 percent of children, immunity has developed by the age of 9. Herpes zoster represents infection in the partially immune host. Whether this is due to reinfection or reactivation has been debated. The latter explanation is favored due to the facts that most persons with zoster have had no recent exposure, that there is no increase in zoster during seasonal peaks of varicella, that the fewest cases of zoster are seen in the groups with the greatest exposure (children and adults in the childbearing ages) and that the antibody response is of the anamnestic type.[1]

From the Ambulatory Care and Medical Services; Portland Veterans Administration Hospital, and the Section of General Medicine, Department of Medicine, University of Oregon Health Sciences Center, Portland.

Submitted May 24, 1978.

Reprint requests to: James B. Reuler, MD, Ambulatory Care Service, Portland Veterans Administration Hospital, 3710 S.W. U.S. Veterans Hospital Road, Portland, OR 97201.

It is postulated that after the initial infection with varicella the virus remains in a latent form in the dorsal root or extramedullary cranial nerve ganglions. At a later date, usually during a time of a decrease in host defenses, the virus is reactivated and spreads retrograde to the skin along sensory nerves. The specific mechanism allowing this reaction has not been delineated. In normal persons high levels of complement fixing antibody develop within the first week of the rash, but there is no relation between antibody level and severity of disease.[2]

Herpes zoster is usually a self-limited disorder seen in otherwise healthy adults after stress. The incidence increases with age with a pronounced increase over the age of 60.[3] Trauma, surgical procedures and arsenic ingestion have been implicated as precipitants. Immunosuppressed persons are at particular risk. In up to 25 percent of persons with Hodgkin disease, herpes zoster will develop and the risk is increased with stages 3 or 4, cutaneous anergy or recent radiation therapy.[4-6] In patients with other lymphomas, leukemia, and congenital and acquired immune deficiencies the incidence is increased.[6,7] Although malignancy may predispose to the development of herpes zoster, zoster is rarely the presenting manifestation of an underlying cancer. Therefore, unless other aspects of the history or physical examination suggest malignancy, it is not necessary to carry out studies for a predisposing tumor in all patients presenting with zoster.[1]

Clinical Manifestations

The hallmark of herpes zoster is the cutaneous eruption, evolving over 4 to 14 days from a macular-papular lesion to vesicles on an erythematous base, either single or grouped, to pustules and finally to crusting. The lesions usually heal rapidly, leaving little scarring, within 5 to 25 days. Histologically the cutaneous lesions of varicella, zoster and herpes simplex are identical and the typical multinucleated giant cell is present which may be readily identified by a Tzanck preparation made from scrapings from the base of the vesicle. The fact that the virus can be cultured from the vesicular fluid for up to seven days raises questions about the risk of transmission to others and the need for isolation of patients with zoster in hospital, although there have been few documented cases of such transmission.

The rash characteristically involves a single dermatome unilaterally, although several contiguous dermatomes may be affected and rarely bilateral involvement may be seen. The dermatomes most frequently involved, in decreasing order, are thoracic, trigeminal, cervical, lumbar and sacral.[3] Headache, malaise, fever and lymphadenopathy may accompany the rash. Pain is a very significant feature of the disease and may precede the rash by up to ten days, leading to confusion with other pain syndromes until the rash appears.

The most frequent complication of herpes zoster is postherpetic neuralgia, defined variously as continued pain in the dermatome after the time that the crusts fall off or as pain lasting beyond six or eight weeks. The incidence is age related, with this complication developing in more than 50 percent of patients older than 60 with zoster.[8] Pain may be so disabling as to lead to suicide. Disseminated zoster, defined by five or more vesicles distant to the primary affected dermatome may be seen in two percent of patients, with a much greater risk in patients having underlying malignancy, and may have associated systemic toxicity.[4,9] Dissemination also implies a poor prognosis for those with malignancy.[4,5] Viral pneumonia, a frequent manifestation of varicella in adults, is a rare complication of disseminated zoster.[10] Cough, dyspnea, fever and hemoptysis within one to six days of the rash are the usual clinical features. Death from respiratory insufficiency may ensue. Meningoencephalitis may precede the rash by up to three weeks and presents with altered mental status, fever and headache, usually in the setting of cranial or cervical dermatome distribution of the rash.[11] Direct invasion of the meninges is the postulated mechanism for the encephalitis, and lymphocytic pleocytosis is frequently present in the cerebrospinal fluid. The usual course is improvement over one to three weeks. Lumbar and sacral root involvement may have associated bladder dysfunction, manifested by retention or symptoms of cystitis.[12] There are reports of this complication preceding the rash and of the presence of vesicles on the bladder wall at cystoscopy. The seventh cranial nerve is the most common motor nerve involvement reflecting the consequence of lymphocytic infiltration and edema along the long bony canal in which the nerve runs. A population of patients with Bell palsy will have elevated zoster titers despite absence of the rash. The Ramsay-Hunt syndrome is characterized by pain in the ear, vesicles localized to the pinna and auditory canal, seventh nerve palsy and frequently associated deafness and vertigo.[13] Other neurological sequelae of herpes zoster include isolated motor paralyses, diaphragmatic, laryngeal and pharyngeal paralysis, ileus, transverse myelitis and the Guillain-Barré syndrome.

Eye complications are of immediate concern in patients with trigeminal nerve involvement. The ophthalmic division with its three branches, frontal, lacrimal and nasociliary, is most commonly involved, with ocular disease developing in 50 percent of these patients. The frontal branch, most frequently affected, innervates the upper lid, forehead and superior conjunctiva. The nasal division of the nasociliary branch innervates the sclera, cornea, iris, ciliary body and the tip of the nose. Therefore, the presence of zoster lesions on the tip of the nose is a harbinger of ocular damage.[14] This involvement may take the form of keratitis, either an acute, self-limited form or a delayed, deforming variety, iritis, episcleritis and secondary glaucoma. Also, extraocular muscle palsies and optic atrophy have been reported.

Therapy

Patients in hospital with herpes zoster should be isolated and every attempt made to avoid exposing other potentially high-risk persons, at least until the vesicular phase has passed, because the virus may be harvested in tissue culture of vesicular fluid. Local skin care using Burrow's

solution to minimize secondary infection and analgesics for pain control are the principal therapeutic manipulations available during the acute phase. Several recent double blind studies have shown idoxuridine, five percent in dimethylsulphoxide (DMSO), applied topically to be efficacious, with shortening of the vesicular phase, healing time and duration of pain.[15-17] Patients with seventh nerve involvement should be referred promptly to an otorhinolaryngologist for evaluation, which should include serial electrical excitablility testing of the nerve. A short course of high-dose oral corticosteroids is indicated in this setting to minimize permanent damage to the nerve.[13] In some cases a surgical decompression procedure may be required to prevent irreversible degeneration. For a patient with evidence of ocular involvement, ophthalmologic evaluation, including intraocular pressures and special corneal staining, is indicated. Mydriatics and topical antibiotics are useful, as are topical corticosteroids, idoxuridine and adenine arabinoside for nonulcerated interstitial keratitis. Systemic steroids may be indicated in the rare patients with refractory uveitis, optic neuritis or proptosis with extraocular muscle palsy.[14]

The major therapeutic challenge facing clinicians is management of postherpetic neuralgia. Multiple therapeutic options, with variable efficacy, are described in the literature and space does not allow for a comprehensive review. Methods utilizing vitamins, local anesthetics, diathermy, radiation, rhizotomy, anticonvulsants, phenothiazines and influenza vaccination have been tried by various authors, with no unanimity of opinion regarding most of these techniques. The role of systemic corticosteroids has been controversial since Merselis reported the cases of 17 patients in whom the disease disseminated, nine of whom had been treated with steroids.[9] Seven of the nine, however, had underlying lymphoma or leukemia. Since then several controlled studies have shown a reduction in the incidence of postherpetic neuralgia, without dissemination, in patients over 60 years old who are given a short course of high dose steroids (40 to 60 mg of prednisone a day) early in the disease;[18,19] initial pain and duration of skin lesions were not altered. Since the usual natural history of herpes zoster is that of complete resolution without sequelae, the use of steroids should be reserved for those patients in the older age groups because these are the patients statistically most likely to be afflicted with postherpetic neuralgia. Systemic corticosteroids should not be administered as therapy for zoster to hosts with compromised defenses or ocular involvement, except in the rare instances previously mentioned.

Other modalities of therapy for herpes zoster in immunodeficient patients have been tried without uniform success. These include transfer factor, gammaglobulin, and idoxuridine. It is important in evaluating therapy to remember that zoster in immunodeficient patients is rarely life threatening. Cytosine arabinoside (ARA-C), originally claimed to be effective in halting progression of disseminated zoster, has been shown in two controlled studies to be ineffective and possibly detrimental,[20,21] Recent data from the collaborative study using adenosine-arabinoside (ARA-A) showed that, if therapy is started within five days in patients less than 38 years old with reticuloendothelial neoplasms, the drug reduced acute pain, accelerated clearance of the virus from vesicles, and speeded healing of the skin lesions.[22] It is not yet clear, however, whether dissemination or postherpetic neuralgia can be aborted. A recent double blind trial of human leukocyte interferon in patients with cancer showed efficacy of high-dose (5.1×10^5 units per kg of body weight per day) interferon in limiting cutaneous dissemination, visceral complications, progression within the primary dermatome and postherpetic neuralgia.[23] Although the results of this study are encouraging, the extremely small worldwide supply of interferon and the difficulty in harvesting it will limit widespread use of this therapeutic modality for the near future. Zoster immune globulin (ZIG), prepared from plasma of patients recovering from zoster, should be reserved for high-risk children with cancer or primary or acquired immune deficiency who have not had varicella and who are exposed to household or other intimate contacts.[24,25] Studies suggest that if ZIG is administered within 72 hours of exposure varicella, although not prevented, will run a milder course than the unmodified illness in the normal host. Because ZIG is difficult to obtain and because zoster may develop in the face of already present antibody titers, its administration is not indicated in the prevention or treatment of zoster.[26-28] Recommendations for use and procurement of ZIG have recently been published by the Center for Disease Control.[29] Recent reports from Japan

have documented effectiveness and innocuousness of a live, attenuated varicella-zoster virus vaccine used to prevent varicella in household and hospital ward contacts.[24,31] Seroconversion without clinical symptoms was documented in all vaccinated children. Further clinical trials of the vaccine on a larger scale have now been advocated.[32]

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Chest Radiography in Intensive Care Units

CHARLES J. SAVOCA, MD; GORDON GAMSU, MD, *and* BARBARA M. ROHLFING, MD,
San Francisco

The role chest radiography plays in intensive care units (ICU) is unlike its role elsewhere because in the ICU a patient's underlying disease is usually known. Furthermore, additional diseases that develop in the ICU—such as pneumonia, hemorrhage, edema, lung collapse and effusion—often are radiographically indistinguishable. Nevertheless, an ICU radiograph of the chest is valuable, mainly in identifying such complications as malpositioned intravenous catheters, Swan-Ganz catheters, pacemakers, nasogastric tubes, endotracheal tubes, chest tubes, and mediastinal tubes, and ectopic gas related to mechanical ventilation. Understanding the limitations of the portable ICU chest film in the diagnosis of specific diseases and being alert to possible iatrogenic complications will increase the usefulness of ICU chest radiography.

THE ROLE of chest radiography in intensive care units (ICU) is unlike its role in most other situations. Because an ICU patient's underlying disease is usually already known, radiology does not contribute to its diagnosis. Furthermore, even when there is diffuse pulmonary consolidation in an ICU patient, the radiographic appearance may not be specific enough to establish the diagnosis. Nevertheless, a radiograph of the chest is very useful in monitoring ICU patients. The clinical and physiologic status of ICU patients is notably deranged and rapidly changing. In addition many complications, due to either the disease process or its treatment, can occur quickly. Correlation between the clinical and radiographic findings is essential to identify and treat these complications.

From the Department of Radiology, University of California, San Francisco.

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Reprint requests to: Charles J. Savoca, MD, 396-M, Department of Radiology, University of California, San Francisco, CA 94143.

Limitations of ICU Chest Radiography

Technical Limitations

At present, most ICU examinations are done at low kilovolt (peak), without grids, and with long exposure time—resulting in high-contrast films with little information about the lung periphery or mediastinum. The long exposure times required often result in motion-blurring, which can simulate the appearance of pulmonary edema and obscure pulmonary consolidation and nodules. Currently in development are phototimed portable machines that use high kV(p), grids, and short exposure time. These should decrease the above mentioned technical limitations.

Other technical limitations will persist, however. The severity of the illness often will not

allow for correct patient positioning. The typical ICU chest radiograph is usually anteroposterior (AP) rather than posteroanterior (PA); this fact makes it difficult to evaluate heart size and to see much of the posterior lung base, which is hidden beneath the dome of the diaphragm. Lateral chest radiographs are difficult to obtain of ICU patients, and without them the problem of visualizing the posterior lung bases is compounded.

The patient's semiupright position also makes evaluation of cardiac status difficult. The upper pulmonary veins are manometers of left-sided venous pressure and the azygos vein is a manometer of right-sided venous pressure and they distend in heart failure. Unfortunately these veins will also distend gravitationally if the patient is supine or only semiupright. The physician must know the exact position in which the film was obtained in order to evaluate the significance of distended azygos or pulmonary veins.

Limitations Due to the Disease Processes

Additional limitations relate to the very nature of the disease processes that occur in ICU patients. Many complications in ICU patients can produce diffuse air-space consolidation, including pulmonary edema, aspiration, infection and hemorrhage. Although such factors as appearance, distribution and time course occasionally allow for an educated guess concerning the cause, none of these findings is sufficiently specific to justify treatment solely based on the radiographic information.

Another limitation of the ICU AP chest radiograph is the difficulty in distinguishing pleural effusion from consolidation or collapse in the posterior lung bases. Adhesive atelectasis in this location is a very common, benign condition in ICU patients that produces increased radiopacity at the lung bases on the AP radiograph. However, this finding can also be produced by pneumonia, aspiration, pulmonary edema, pleural effusion, empyema or hemothorax. Lateral decubitus films often allow for distinction between these conditions. Both lateral decubitus views should be taken routinely in such cases. The film obtained with the patient's affected side down permits evaluation of pleural fluid. The radiograph obtained with the patient's affected side up shows the involved lung during greatest aeration and commonly helps in differentiating collapse from consolidation.

Value of ICU Chest Radiography

Probably the most important function of ICU radiography is to identify complications that can result from either the disease or its treatment. Complications of treatment frequently are due to malposition of catheters, tubes and pacemakers. Therefore, it is a good practice to scrutinize these devices before concentrating on the appearance of the heart and lungs.

The most common catheters are those used for intravenous infusion or central venous pressure monitoring. These are usually placed by means of puncture in a jugular or subclavian vein. Complications of subclavian puncture include hemorrhage into the extrapleural and mediastinal spaces and pneumothorax. Complications also result from improper position of the catheter. The intravascular course is generally through a brachio-

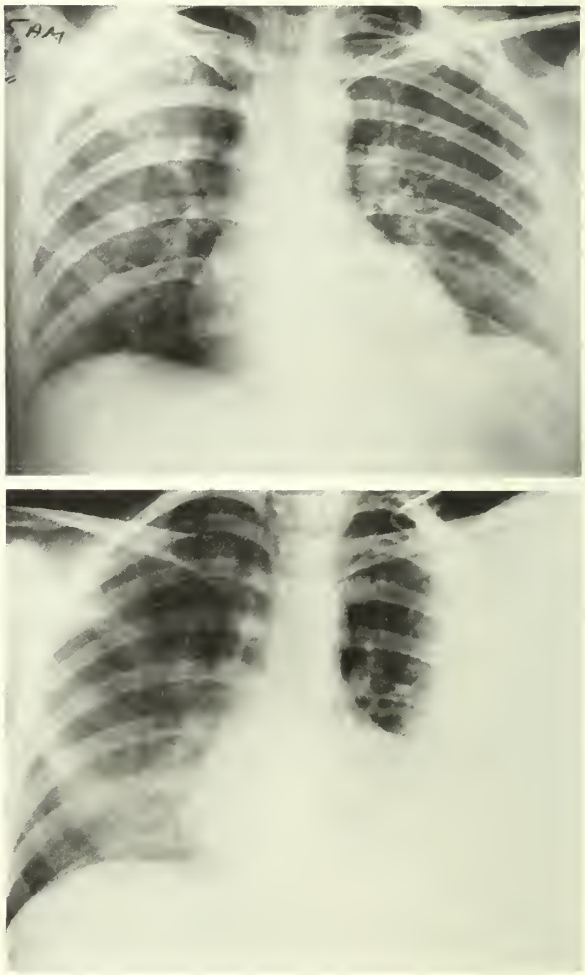

Figure 1.—Top, Subclavian catheter located abnormally to left of the spine. Left lateral decubitus radiograph taken 30 minutes later **(bottom)** showing extravascular position and intravenous fluid in left pleural space.

cephalic vein to the right superior vena cava (SVC). Other, more unusual, locations are the azygos vein,[1] internal jugular vein, hepatic vein,[2] internal mammary vein, pericardiophrenic vein[3] and persistent left SVC.[4] If the catheter is not visualized in these locations, it may be extravascular. Identification of this complication may prevent excessive instillation of intravenous fluid into the mediastinum or pleural space (Figure 1).

Another intravenous catheter employed in the ICU is the Swan-Ganz pressure-monitoring catheter. The main complication that occurs with use of Swan-Ganz catheters is pulmonary infarction from obstruction of a pulmonary artery.[5] It can result from failure to deflate the balloon or excessively peripheral placement of the catheter tip; both of these causes can be identified on the chest radiograph, and the infarction averted (Figure 2).

Transvenous pacemaker leads have their own radiographically visible problems. The most common are dislodgment of the tip and malposition into the coronary sinus system. The normal pacemaker has a gentle downward curve on frontal projections and points anteriorly on lateral projections. A malpositioned lead frequently has an unusual kink as it enters the coronary sinus. On lateral views, the posterior position of the tip often confirms the diagnosis. Unfortunately, if the pacemaker is in the middle coronary vein it may still project anteriorly. Almost all leads in the coronary sinus will pace the left ventricle. On an electrocardiogram this pacing gives the same findings as a right bundle branch block. The electrocardiogram can therefore confirm the radiographic impression. A rare, but serious, complication of pacemaker leads is perforation of the myocardium (Figure 3), which can lead to hemopericardium and tamponade.

Figure 2.—Balloon **(arrows)** that was left inflated at tip of Swan-Ganz catheter. Radiopacity extending from this balloon may represent atelectasis, hemorrhage or infarction.

Nasogastric tubes can curl within the hypopharynx or esophagus. If the tip is not in the stomach, then gastric distention and, in turn, aspiration may result. The tip can also enter the airway. Because semiconscious patients sometimes tolerate this malposition, the radiograph may be the best means of identifying the complication. If it is not identified, tube feedings can be instilled into the lung (Figure 4).

In a patient receiving mechanical ventilation, the major problem is a malpositioned tip of the endotracheal tube. Because of the anatomy of the bronchial tree, the tube tip often enters the right main bronchus or bronchus intermedius. Although this may cause no visible abnormality, presumably because both lungs continue to be ventilated, obstruction to the right upper lobe or left lung or both can sometimes develop (Figure 5). Less commonly the tip enters the left main bronchus, obstructing the right lung. Consequently, the location of the tip of the endotracheal tube must be checked on every radiograph of a mechanically ventilated patient. From extension of the neck to flexion, the tip can move as much as 6 cm; it should therefore be kept at least 2 to 3 cm above the carina in adults.

A delayed complication of mechanical ventilation is tracheal stenosis, which can result from trauma to the tracheal wall by malalignment of the tip of the endotracheal tube or hyperinflation of its cuff. Both can generally be identified on the radiograph and the complication thus averted.

Ectopic gas is another complication related to mechanical ventilation.[6] It can take the form of pulmonary interstitial emphysema, pneumomediastinum, pneumothorax, pneumopericardium, subcutaneous emphysema, pneumoretroperitoneum or pneumoperitoneum. The most common cause of ectopic gas is high transpulmonary pressure, which is often necessary to ventilate the lungs of ICU patients. Less common causes of ectopic gas are endotracheal tube obstruction,

intubation beyond the carina and manual ventilation. Once an alveolus or bronchiole has ruptured, gas dissects into the interstitium and tracks back along peribronchial and perivascular sheaths to the mediastinum.[7] From the mediastinum, the gas can break into the pleural space to become pneumothorax, or it can break into the pericardial space to become pneumopericardium. Within the fascial plane of the mediastinum, gas can dissect in many directions and have many different radiographic appearances. It can dissect superiorly into the neck and over the chest wall to become subcutaneous emphysema. It can also dissect over the apex of the lungs beneath the ribs or beneath the base of the lungs above the diaphragm to become extrapleural gas; in these locations, the

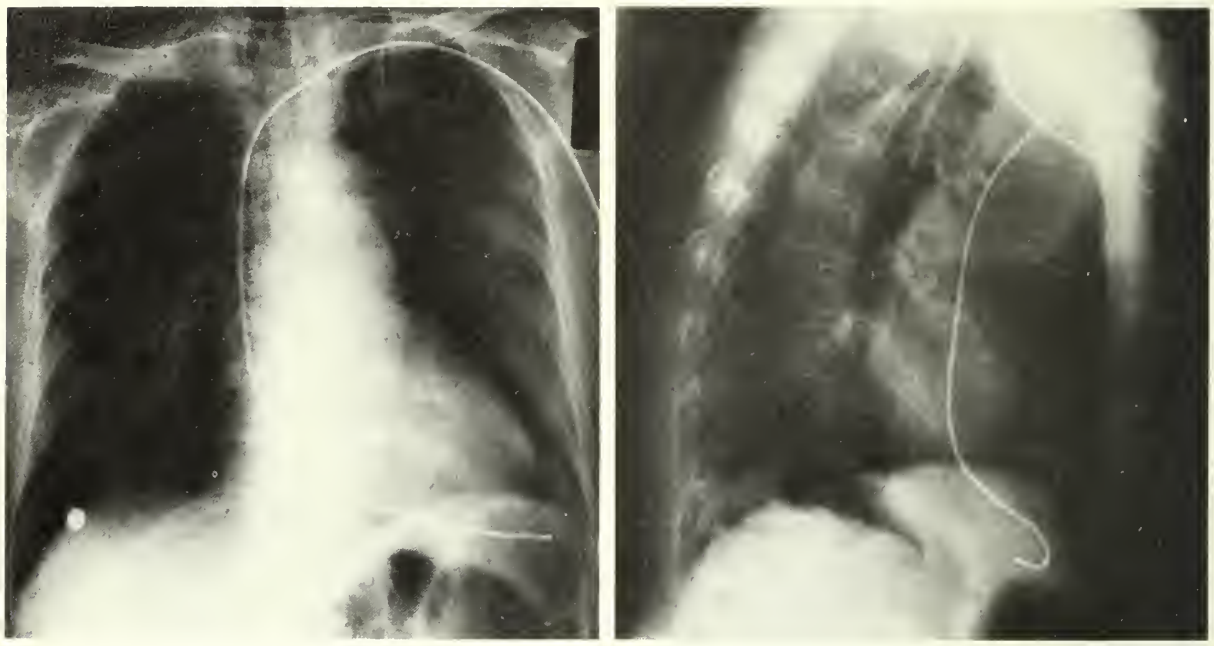

Figure 3.—Noncapturing pacemaker that was pacing the diaphragm. Frontal film **(left)** showing tip of catheter at the left cardiac margin, beyond the expected position at the intraventricular septum. Lateral film **(right)** showing pacemaker wire deflected posteriorly, confirming that it has perforated out to the pericardial sac.

Figure 4.—**Left,** Marker on the nasogastric tube seen over left lung. **Right,** Before malposition was appreciated, tube feedings infused into left lower lobe.

gas can be confused with pneumothorax. The gas can also dissect below the diaphragm, where it disperses over the posterior abdominal wall to become pneumoretroperitoneum, or along the under surfaces of the diaphragm, where it can be confused with pneumoperitoneum. Finally, gas in the retroperitoneal space can break through the parietal peritoneum to become pneumoperitoneum.

Figure 5.—Endotracheal tube tip **(arrow)** in right main bronchus obstructing left lung and shifting mediastinum towards left

It is extremely important to distinguish pneumothorax (which requires a chest tube) and pneumoperitoneum (which may signify a ruptured viscus) from other forms of ectopic gas (which usually do not require treatment). Making this distinction from a routine ICU chest radiograph can be difficult. Ectopic gas seen between the bottom of the right lung and the top of the liver typifies the diagnostic problems that can arise. Five types of ectopic gas can develop in this region. The most cephalic is interstitial emphysema, in the form of a subpleural bleb at the lung base. Immediately caudad lies the pleural space where subpulmonic pneumothorax can occur. Beneath the parietal pleura, ectopic gas can collect in the extrapleural space. Beneath the diaphragm but above the parietal peritoneum, ectopic gas can collect in the retroperitoneal space. Finally, beneath the parietal peritoneum but above the liver, ectopic gas can collect as pneumoperitoneum.

On the frontal radiograph all five types of ectopic gas may be indistinguishable, appearing

Figure 6.—**Left,** Nonfunctioning chest tube having only a short section beyond its apparent turn beneath ribs. Gastric distention is present. **Right,** Oblique film obtained after tube was advanced showing that tube dissected above ribs and was not in the pleural space.

Figure 7.—A subxyphoid mediastinal tube which resisted removal. Whether tube was entrapped could not be determined from the anteroposterior projection. The lateral film faintly shows posterior wall of tube **(arrows)** entrapped by uppermost suture.

as concentric lucencies—that is, conforming to the shape of the diaphragm. Fortunately, a decubitus view with the patient's affected side up will distinguish among these five conditions. The air in pneumothorax will rise under the lateral chest wall; in pneumoperitoneum it will rise under the lateral abdominal wall. In the other three forms, ectopic gas does not flow easily and its position will generally remain unchanged.

For ICU patients being treated with pleural chest tubes, radiographic assessment may avert complications. The mere presence of a chest tube does not guarantee evacuation of the pleural space; the tip can become plugged or a side-hole may be outside the chest. The chest tube sometimes, although rarely, lies along the chest wall, above rather than beneath the ribs. An oblique film may be necessary to identify this malposition (Figure 6).

Drainage tubes are frequently placed in the mediastinum at the time of cardiac surgical procedures. Despite the fact that these tubes are placed beneath the sternal wire sutures under direct vision, they occasionally become entrapped during closure[8] (Figure 7).

Comment

Having allowed for the limitations of ICU chest radiography and having checked carefully all catheters and tubes with particular attention to possible iatrogenic complications, one may proceed with the more routine radiographic analysis of the heart and lungs. Close correlation between the clinical and radiographic findings greatly facilitates detection and treatment of complications that may develop in patients in intensive care units.

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Specialty Conference

Participants
HECTOR E. JAMES, MD
WILLIAM L. NYHAN, MD, PhD

From the Department of Surgery, Division of Neurosurgery and Department of Pediatrics, University of California San Diego and the University of California Medical Center, San Diego.

Refer to: James HE, Nyhan WL: Spinal dysraphism—An interdisciplinary diagnostic approach—University of California, San Diego, and the University of California Medical Center, San Diego (Specialty Conference). West J Med 129:475-479 Dec 1978

Spinal Dysraphism

An Interdisciplinary Diagnostic Approach

WILLIAM L. NYHAN, MD, PHD:* *I am pleased to introduce Dr. Hector James, who is Assistant Professor of Neurosurgery and Pediatrics. He joined the faculty at the University of California, San Diego, this year and is the director of Pediatric Neurosurgery. He is going to speak on spinal dysraphism.*

HECTOR E. JAMES, MD:† I would like to cover this topic by defining the clinical entities, the clinical presentation of the syndromes, a comprehensive diagnostic approach using new modalities, and finally therapy.

Under the term spinal dysraphism popularized by Lichtenstein[1] one can place a large family of disorders. However, common usage, primarily in Great Britain, has been to reserve the term for pathologic conditions of the spine that are not overt, excluding myelomeningocele, for instance, or spina bifida cystica. The term implies a problem that presents primarily as an occult syndrome, a disorder that is not evident at birth unless specifically sought. The pathogenesis and the clinical syndromes have been well defined by James and Lassman.[2]

Pathogenesis may occur in two different forms. One is the *pressure group*. If, for instance, a lipoma is growing inside the spinal canal there will be a dysfunction of the conus medullaris or nerve roots because of compression in the rigid canal of the neural elements, as the mass continues growing inside it. The other is the *traction group*. Normally the spinal cord migrates with age because of differential rates of growth between the spinal column and the spinal cord itself. If this migration is interfered with, traction of the neural elements of the conus medullaris and spinal cord can occur. From Barson's[3] analysis of the position of the conus medullaris in the spinal canal of human fetuses at different stages of gestation, the normal adult position for the conus medullaris is not reached until after birth. There is a progressive migration of the conus medullaris during gestation because the spinal column is growing at a much faster rate than the spinal cord. The final position of the conus medullaris may not be reached until the fourth or fifth year of life. What types of pathologic conditions can interrupt this migration? In Tills'[4] series the vast majority are situations in which there is tethering of the conus. When this happens there is traction from the filum terminale to the conus medullaris and normal migration is impaired. Next most common is diastematomyelia. In this condition a spicule of bone or connective tissue without bone transects the spinal canal from its ventral to dorsal aspect, and in so doing transects the spinal cord and restricts rostral migration. In Matson's[5] series, the most common site is in the lumbar region; more rarely it occurs in the thoracic region.

Clinical Presentation

James and Lassman[2] defined two major clinical presentations, though combinations of both in

*Professor and Chairman, Department of Pediatrics.

†Assistant Professor of Neurosurgery and Pediatrics.

Reprint requests to: Hector E. James, MD, Director, Pediatric Neurosurgery, University of California San Diego, P.O. Box 3548, San Diego, CA 92103.

TABLE 1.—*Spinal Dysraphism*

Clinical syndrome
Characteristically slow clinical course
Orthopedic syndrome
Cutaneous anomalies (may be present)
Asymmetry of legs
Diminished muscle bulk
Shortened foot
Inversion of foot, pes cavus, elevation of the first metatarsal head, clawing of toes
Peculiar gait
Reflex changes may be present, usually late
Urological syndrome
Bladder changes: alterations in urinary frequency, retension, incontinence
With or without bowel symptoms
With or without cutaneous lesions
Tethered cord syndrome
Terminology used to cover the above spectrum

which one or the other is dominant are more common (Table 1). The first is the orthopedic syndrome in which there are cutaneous anomalies such as exuberant growth of hair, telangiectasis, or a small lipoma underneath the skin—something that will signal the disorder below it. Asymmetry of the legs is characteristic. There is diminished muscle bulk and a shortened foot. When you look closely at the foot you may find the following: inversion of the foot, a pes cavus deformity, elevation of the metatarsal head, or clawing of the toes. These changes result from an imbalance between agonist and antagonist muscles.

The second is the urological syndrome. In a child with a previously normal voiding pattern and continence, a disorder subsequently develops in which there is frequency of urination or incontinence, or repeated urinary tract infections occur not readily explained by urologists. Designation of the syndromes in this way[2] is useful because it alerts us to the populations of patients that should be considered for this diagnosis. A child with the orthopedic syndrome is usually referred from the pediatrician or the family practice physician to the orthopedic surgeon, who lengthens or shortens tendons to make the limb look better. Finally, when the disorder progresses despite surgical procedures the child is referred to a neurosurgeon. The child with the urological syndrome is commonly referred to a urologist because of an abnormality in voiding pattern or urinary tract infections. After repeated normal findings on cystoscopies and radiologic studies, it finally becomes apparent that something is wrong with the innervation of the bladder and sphincter mechanism.

Unfortunately we tend in medical education to emphasize those things that are common and, often, obvious. Among the disorders of the spinal cord, therefore, we devote considerable attention to myelomeningocele and related conditions that are easy to diagnose. A general physician, orthopedist or urologist often has had no experience with the disorders we are discussing today, and he may not have been taught that they exist. Therefore the patient often reaches a neurosurgeon late in the disease. In reality these are the conditions we want to see the earliest, because it is at that time that therapy is of most value. We are dealing with central nervous system axons and neurons and damage once done is frequently irreversible. The value of corrective surgical therapy is that it prevents progression.[4,6] I will present two cases as examples of this.

Case 1. The mother of a 5-year-old boy had noted when the child was 6 months old that there was an asymmetry of the lower extremities. As commonly happens, she was not listened to. We saw the child after two tendon procedures had been done. The form of presentation, therefore, was the orthopedic syndrome. The findings were wasting of the gastrocnemius on one side and gross asymmetry of the feet, one being smaller than the other. When we looked more closely at the smaller foot we could see a pes cavus deformity, elevation of the first metatarsal head and clawing of the toes. He had a diastematomyelia.

Case 2. The patient was seen at birth by two physicians who insisted, contrary to the mother's view, that the child's footprints were normal. The boy finally was brought to a pediatrician who referred him to us. There was no doubt that the mother was correct. There was something wrong with the footprint. The footprint was that of a patient with the orthopedic syndrome. There was a cavus deformity with a lack of imprint in the area of the elevated head of the first metatarsal, and the toes came down as a claw. This child had a filum terminale tethered to a skin dimple in the coccygeal region.

One must differentiate these disorders that are more common from another group of disorders called spinal hamartomas.[7] These latter present very commonly with a lump in the back, and the differential diagnosis ranges from myelomeningo-

cele which is not possible because the skin is intact, to sacrococcygeal teratoma. The growths are called hamartomas because the tissue inside them is adult mature tissue; it is simply out of its proper place. Palpable bone may be felt in the mass. Results of neurological examination at birth may be normal. We have warned[7] that if the entity is not promptly treated traction can occur. Surgical therapy, therefore, is indicated for these hamartomatous conditions.

Diagnosis

Clinical findings, history and physical examination are as always imperative elements in coming to the diagnosis. The diagnostic studies that are done routinely include x-ray studies of the spine. One may see a variety of things in the spine, abnormal structures with punched out areas in the lamina where mesodermal fusion in the midline was inadequate, or a slightly widened spinal canal with a spicule of bone inside it. This is the classic appearance of diastematomyelia. If it is present, no further studies are needed. Unfortunately there is so much cartilage in this area and poorly calcified bone in a young child that the radiological report is often that of a normal spine, because the anomaly cannot be seen. Myelography has been the classical approach to the diagnosis of intraspinal problems but we are getting away from it. Pediatricians do not like to refer children for invasive procedures, and I agree with them. Then, to do a myelogram in a child, general anesthesia is often required. Also, most radiologists have had little experience with the performance of myelograms in children because this procedure is not often done. Finally, there may be a very low-set conus medullaris, and a lumbar puncture and injection of contrast agent may be a dangerous way to study the area. Alternatively, if one tries the cisternal route or the lateral cervical approach, there could be the problem of an Arnold-Chiari malformation and a descended brain stem, and again harm could occur.[8]

It became evident to us that the techniques employed in the diagnosis of these syndromes were not at all satisfactory. In the presence of an enormously distended bladder, there is no problem leading one to suspect a neurologic abnormality. It is in borderline situations that one needs help for early detection. There are usually no significant changes in findings on the intravenous pyelogram. Fortunately the urologist can be of assistance using urodynamic studies. These consist in the monitoring of the rectal sphincter tone and the rectal electromyogram (EMG), simultaneously with the filling of the bladder, the classical cystometrogram. The method employs a catheter with a double lumen; one lumen is to inject air to inflate the bladder and the other is to record pressure. At the same time, as the catheter is pulled out using timed technique, one can monitor the pressure of the internal and external sphincters. Since the dermatomes that innervate the rectal sphincter also innervate the sphincter of the bladder, one may see if the reflex arc is intact or if it is impaired. With the advent of this technique, we began to detect problems very early in their development.

The other factor that needed improvement was the diagnosis of changes inside the spinal canal, preferably using a noninvasive procedure. The advent of computer tomography (CT) has permitted this. CT can assess the type of tissue we are dealing with using what are called the Hounsfield numbers. These are the quantitative representation of the density of absorption of the radiation source. As computer technology improved, magnification of CT scans became feasible. We then looked at the myelographic criteria that were used to diagnose a tethered conus. Gryspeerdt[8] defined three primary criteria: a low position of the conus medullaris; a dorsally located filum terminale (normally there is lumbar lordosis and if the filum is tethered because of the curvature of the spine, it will be located in the dorsal aspect of the canal), and, finally, a filum terminale that has a width greater than 2 mm.

With these criteria we proceeded to study the CT data. We had an unusual opportunity with a two-year-old girl whose foster mother became quite concerned because the child started to walk late. Moreover, when the child did start to walk she had an obvious limp on the left. The same pediatrician that referred the previous child with the abnormal footprint saw her, found a sacral skin dimple, and referred her as a potential patient with a tethered cord. We noted a smaller foot and smaller muscle bulk of the gastrocnemius on the left side. Her bowel and bladder function seemed to be intact and passed urodynamic testing. Roentgenograms of the spine showed some widening of the lumbosacral junction and of the sacrum itself, though they had

been reported as normal. A CT of the spine was requested. In the study we could see the iliac crest, the sacrum, the bifid sacrum heralding a mesodermal disorder, and a structure inside the sacrum at S1 which should not have been there. We then set the scanner so that the computer would analyze the tissue that was in the sacrum, and it indicated that it was fat. We then analyzed the tissue inside the round element that was in the canal, and the computer read 16 Hounsfield units, which indicated fibrous or glial tissue

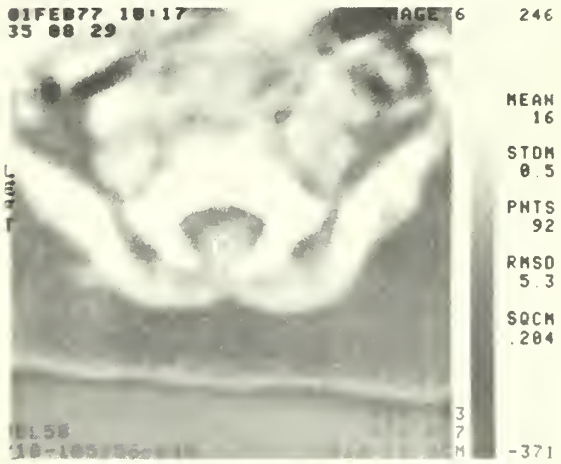

Figure 1.—Computer tomography scan through the upper sacrum. There is a rounded structure, dorsally located and forming a unit with the midline defect of the lamina. The Cursor reading of the scanner identifies fibrous-glial tissue (16 Hounsfield units, upper right corner). (Reproduced by permission from James HE, Oliff M: Computer tomography in spinal dysraphism. J Computer Assisted Tomography 1:391-397, 1977, Raven Press, New York.)

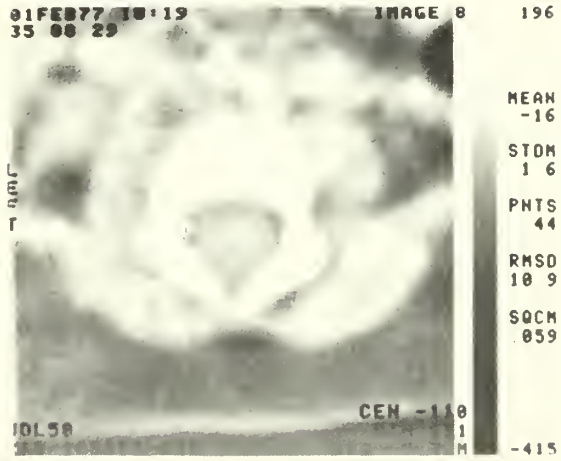

Figure 2.—Computer tomography scan of the same patient as in Figure 1, at the L4 level, showing a low set conus in the spinal canal, allowing little room for the normally extensive epidural fat (Cursor reading: −16 Hounsfield units, upper right corner).

(Figures 1 and 2). We then had a rounded structure that was centrally and slightly dorsally located in the sacrum that was continuous with the defect in the back of the sacrum. We therefore had the first two of Gryspeerdt's criteria.[8] There is nothing that should be rounded, plump and located dorsally in the canal except a thickened filum terminale. What we would like next is the third criterion, that is its transverse diameter. So we turned the computer to what is called the "F" series, which allows us to measure between two points on each side of the filum, and it read 8.93 mm. Anything measuring more than 2 mm is a thickened filum. At operation we confirmed these findings. We sectioned the filum terminale at its point of attachment.

Let us discuss two more examples.

CASE 3. An adolescent had an absent ankle jerk on the left, wasting of the left gastrocnemius, and a lump off the midline in the sacral area. On CT examination the normal paraspinal musculature, subcutaneous fat and a bifid vertebral body at the level of L5 were evident. The paraspinal muscles were no longer symmetrical, and there was a local increase in subcutaneous fat. The upper sacrum was bifid, and we could follow the subcutaneous fat into the area of the canal. This was a leptomyelipoma in a bifid spine, an occult presentation of a lipoma that was tethering the cord and invading the spinal canal.

CASE 4. The next case was a 9-month-old child of a diabetic mother. The child had a peculiar looking pelvis, as well as wasting of one foot and of the gastrocnemius on one side. It was felt that the child had a pathologic condition of the spinal cord. On roentgenographic examination the iliac crests were close together, indicating an agenesis of the sacrum. The CT scans started at L2 and proceeded down into the sacrum. We saw a remarkable narrowing of the spinal canal. These children can have lumbar stenosis and compression of the nerve roots and conus medullaris. As the study continued the normal vertebral bodies disappeared, and we could see the iliac crests on each side. Bone had been replaced by fat.

In summary, what has been attained over the past several years is an interdisciplinary approach to the recognition of the clinical entity and the application of new techniques in urology and radiology.[9] We now have a noninvasive diagnostic approach which facilitates early appropriate therapy for this disease.

DR. NYHAN: *Are there questions?*

QUESTION: *Would you carry out studies in every child with a sacral dimple?*

DR. JAMES: That is a very good question. In the article by Powell and associates[10] a large number of children with dimples were studied and only two or three had any neurological problem. The dimple becomes important when there is evidence of any of the clinical components of either the urological or the orthopedic syndromes. We do not do tests in every child with a dimple in the back, but what we do is listen to the mother's story and examine the child. If the question is then still present there is no reason why further studies should not be done.

QUESTION: *How about children with midline lumbar or sacral masses?*

DR. JAMES: If there is any sort of lump I would become extremely concerned. That is a clear heralding sign of an underlying mesodermal disorder. The ectoderm can have disorders on its own without significant underlying problems. The mesoderm seems to be the primary component in all of these disorders. Any child with a lump in this area needs a thorough evaluation.

One thing I would like to mention in closing is that until June 1977 we had placed these disease entities in a separate category from those of myelomeningoceles. There is now new information on the familial incidence of these diseases. At the June 1977 meeting of the International Society for Pediatric Neurosurgery, Till[11] stated that statistical analyses from London showed a higher incidence of dysraphic disorders, including myelomeningoceles, in families in which there have been occult forms of dysraphism. Alpha-fetoprotein determination on amniotic fluid is now recommended in subsequent pregnancies in these families.

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Refer to: Legionnaires' disease—Medical Staff Conference, University of California, San Francisco. West J Med 129: 480-485, Dec 1978

Legionnaires' Disease

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and Robert C. Siegel, Associate Professor of Medicine and Orthopaedic Surgery, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *The subject of this Medical Staff Conference is Legionnaires' disease. The discussant is Dr. Barbara Kirby. Dr. Kirby received her undergraduate degree from Stanford and her medical degree from the University of Washington. She then came to the University of California, San Francisco, for internship and residency training. At present, she is an infectious disease fellow at Wadsworth Veterans Hospital in Los Angeles, and has had the opportunity recently to participate in the investigation of an important outbreak of Legionnaires' disease.*

DR. KIRBY:† Thank you, Dr. Smith. In July 1976 acute febrile respiratory illnesses developed in 182 persons attending conventions in Philadelphia; 29 died.[1] Because most of these persons were attending an American Legion convention, the disease is now known as Legionnaires' disease. In the ensuing two years, a great deal has been learned about what was then a mysterious and frightening occurrence. It is now known that Legionnaires' disease is caused by a bacterium, an as yet unclassified Gram-negative organism.[2] The organism probably comes from an environmental source, such as soil or water. Transmission is presumably airborne, through aerosolization of soil, dust, or contaminated water. Person-to-person transmission has not been seen; consequently, a patient with suspected Legionnaires' disease need not be placed in isolation. The usual incubation period is two to ten days.

Since 1976 several hundred sporadic cases of Legionnaires' disease have been reported. However, most reported cases have occurred in clusters. Retrospective analyses of sera saved from previously undiagnosed outbreaks of respiratory illness have confirmed the occurrences of Legionnaires' disease since 1965. In that year, in St. Elizabeth's Psychiatric Institute in Washington, D.C., the disease developed in 81 patients; 12 died. Three years later, in a state health department in Pontiac, Michigan, 144 people became ill; none died. Since 1973 a number of outbreaks have occurred throughout the world. These include outbreaks in Spain, England and, in the United States, in Philadelphia; Burlington, Vermont; Kingsport, Tennessee; Columbus, Ohio; Bloomington, Indiana; New York and Los Angeles. With the exception of the Los Angeles outbreak, most outbreaks in the United States have occurred in summer and have been short-lived. The outbreaks have usually been associated with specific buildings. Frequently there has been nearby excavation or construction which pre-

*Lloyd H. Smith, Jr, MD, Professor and Chairman, Department of Medicine.

†Barbara Kirby, MD, Fellow in Infectious Diseases, Wadsworth Veterans Administration Hospital Center, Los Angeles.

TABLE 1.—*Underlying Disease in 24 Patients with Legionnaires' Disease*

		Total
Immunosuppression		9
Renal transplant recipient	4	
Steroid-dependent asthma	2	
Vasculitis	1	
Lymphoma	1	
Laryngeal edema	1	
Skin disease (topical steroids)		2
Cardiorespiratory disease		7
Chronic renal failure		1
Sickle cell anemia		1
Alcoholic hepatitis		1
None		3
		24

sumably has allowed spread of the organism from the soil to the building. In addition to the two mentioned above, other specific buildings associated with outbreaks include the Bellevue-Stratford hotel in Philadephia in which outbreaks occurred in 1974 and 1976, a dormitory in Indiana, and the recently built Wadsworth Veterans Administration hospital in Los Angeles.

The outbreak in Los Angeles is the first outbreak in the western United States.[3] The hospital was opened in March 1977. The first case was identified in May 1977, and cases have continued to occur, without seasonal variation, for the past 14 months. Epidemiologic evidence strongly suggests that Legionnaires' disease in this outbreak is nosocomially acquired.[4] There is a statistically significant incidence of seropositivity among hospital employees and groundskeepers compared to federal employees in an adjacent building. The average number of days between admission to the hospital and onset of illness is 19. When this is compared to the usual incubation period of two to ten days, the implication is clear: patients are exposed while they are in the hospital. In addition, Legionnaires' disease has not been documented in other parts of Los Angeles.

Because this is a nosocomial outbreak, with diseases occurring in patients already admitted to hospital, most patients have significant underlying diseases. Table 1 is a summary of the underlying diseases in the first 24 patients with Legionnaires' disease seen in our hospital. Nine of the 24 had underlying disorders for which immunosuppressive therapy was required. All of these were given pharmacologic doses of corticosteroids; five also received azathioprine. Because Legionnaires' disease developed in more than half of the patients who received renal transplants in the new hospital, the transplantation program has been suspended. In addition to the nine patients who received oral or parenteral steroids, two other patients had extensive skin disease for which they were given large amounts of topical steroid. Clearly, immunosuppressed patients are at risk. Patients with cardiorespiratory diseases made up the second largest group. Three patients, all employees, had no underlying diseases.

Signs and Symptoms

Before discussing the specific signs and symptoms of Legionnaires' disease, I will present a general overview of the clinical presentation because there is not yet an easy, reliable method of diagnosing the disease during the acute illness. In our experience, there is a characteristic symptom complex which allows an early presumptive diagnosis and the institution of specific, perhaps lifesaving, therapy. Typically, low grade temperature elevation to levels of 38°C (100°F to 101°F) is noted on routine vital signs. The house officer is called and finds a patient who appears well and denies symptoms. If pressed, the patient may admit to some weakness, malaise or anorexia. Except for temperature elevation, findings on physical examination are usually normal. In a few instances, rales may be noted this early in the illness. If the fever workup includes a radiograph of the chest, a patchy alveolar infiltrate is frequently noted even though the patient has no cough and no abnormalities are seen on physical examination.

Over the next one or two days dramatic changes occur. Typically, there is a stepwise increase in temperature to levels of 39°C (103°F) or greater. Frequently the heart rate is disproportionately slow for the degree of temperature elevation. The patient is diaphoretic and may be confused. Rales are noted on examination of the chest. The characteristic symptoms of dry cough, recurrent rigors, diarrhea and pleuritic pain appear by the second or third day of illness.

Table 2 is a summary of the main clinical symptoms of Legionnaires' disease. Anorexia, malaise and profound weakness are universal symptoms but are certainly not specific. Cough is uniformly present, but it is often so subtle that the patient may not complain of it. Coughing is

TABLE 2.—*Clinical Symptoms in Legionnaires' Disease**

	Incidence (Percent)
Cough	100
Rigors	88
Diarrhea	54
Pleuritic pain	42
Nausea	29
Headache	25
Vomiting	20
Myalgia	17
Rhinitis, laryngitis	12

*24 patients

TABLE 3.—*Clinical Signs of Legionnaires' Disease**

	Incidence (Percent)
Maximum temperature	
≥40.5°C (≥105°F)	32
40°C-40.5°C (104°F-105°F)	40
39.4°C-40°C (103°F-104°F)	27
Relative bradycardia	59
Disorientation	33

*22 patients

initially dry and not hacking; it does not keep the patient awake at night. After the third or fourth day of illness, the cough becomes productive in about two thirds of patients. The sputum produced is nonpurulent and frequently is blood-tinged. The absence of grossly purulent sputum in a patient who clinically and radiographically has a bacterial pneumonia is an important observation. The patient begins to have shaking chills on the second or third day of illness. The chills are characteristically recurrent. Diarrhea is usually an early symptom and may, in fact, predate the onset of fever; it is watery, without blood or mucus, and is not accompanied by abdominal cramping or other pain. Pleuritic pain is the fourth major symptom. Pleuritic pain, coupled with high fever, pulmonary infiltrate and cough productive of blood-tinged sputum in a patient in hospital frequently suggests the diagnosis of pulmonary infarction. In five patients in our series, pulmonary angiography was done because pulmonary infarction was so high on the differential diagnosis. Headache, myalgias, nausea, vomiting, and rhinitis and laryngitis occur less frequently and are less helpful clues to the diagnosis.

The clinical signs of Legionnaires' disease are listed on Table 3. No patient had a maximum temperature of less than 39.4°C (103°F) and a third had temperatures in excess of 40.5°C (105°F). A significant proportion were immunosuppressed; however, immunosuppression did not appear to interfere with the ability to generate this impressive febrile response. Once the temperature reaches maximum levels, it becomes continuous or only mildly remittent. With antipyretic therapy, the temperature may be reduced temporarily by one or two degrees, but it rapidly returns to the high level. Relative bradycardia, by which I mean a heart rate of 100 beats per minute or less in association with a temperature of 39.4°C or greater, is a helpful finding and is often quite dramatic. Disorientation is seen in a third of patients; we did not note hallucinations or focal neurologic findings in our series; however, these have been reported.[5] In addition to overt confusion, other neurologic manifestations sometimes seen include emotional lability, depression and retrograde amnesia.

TABLE 4.—*Laboratory Findings in Legionnaires' Disease**

	Incidence (Percent)
↑Leukocytes >14,000 per cu mm	67
↑SGOT (Range 64-241 IU per liter)	53
↑Alkaline phosphatase (Range 106-805 IU per liter)	52
↑LDH (Range 244-800 IU per liter)	100
↑Bilirubin (Range 1.6-4.5 mg per dl)	24
Hyponatremia (Range 121-129 mEq per liter)	66
Hypophosphatemia (Range 1.2-2.4 mg per dl)	57

SGOT = serum glutamic oxaloacetic transaminase
LDH = lactic dehydrogenase

*22 patients

Laboratory findings are summarized on Table 4. Leukocytosis is typical. Mild to moderate elevation in hepatic enzymes and bilirubin is noted early in the illness and tends to resolve over several weeks. Hyponatremia occurs in two thirds of patients; simultaneous serum and urine osmolalities and electrolytes may support the diagnosis of the syndrome of inappropriate antidiuretic hormone secretion. The most intriguing laboratory abnormality is hypophosphatemia. This occurs early in the illness and can not be ascribed to the usual causes of hypophosphatemia. Hypophosphatemia in association with Gram-negative and, less frequently, Gram-positive septicemia has been reported. Although bacteremia has not yet been shown to occur in Legionnaires' disease, it is tempting to speculate that bacteremia is the cause of the observed hypophosphatemia.

Examination of sputum is important. Gram stain of sputum obtained by transtracheal aspira-

tion in patients with Legionnaires' disease shows few to moderate numbers of polymorphonuclear leukocytes and no organisms. Although the agent of Legionnaires' disease is a Gram-negative bacterium, it does not take up the stain well in clinical specimens, and the Gram stain is, therefore, typically negative. The small numbers of leukocytes and the absence of organisms are helpful in ruling out other bacterial pathogens.

No radiographic finding in Legionnaires' disease is pathognomonic, however, several general remarks can be made. The initial radiograph, if obtained early in the course, shows a unilobar patchy alveolar infiltrate. Progression may involve one of three patterns: (1) consolidation in the area of the initial infiltrate, (2) persistence of the initial infiltrate and appearance of new infiltrates or (3) resolution of the initial infiltrate and appearance of new infiltrates. Any lobe may be involved, but lower lobe involvement is the most common. Small pleural effusions are seen in at least half of cases and, in a few instances, the effusion has predated radiographic evidence of parenchymal infiltrate. Cavitation is not seen. Radiographic improvement is noted within two weeks in most patients treated with erythromycin. In patients who are not treated with erythromycin, but survive, radiographic abnormalities may persist for months.

Three cases will be presented to emphasize the clinical and radiographic features.

Figure 1.—Diffuse alveolar infiltrate in a 55-year-old women (case 1).

Reports of Cases

CASE 1. A 55-year-old woman, an employee with a 100 pack-year* smoking history, was admitted with a three-day history of profound weakness, anorexia, cough, fever and chills. The shaking chills were recurrent and the cough was productive of a small amount of rusty sputum. On physical examination, the patient appeared acutely ill but was oriented. Body temperature was 39.6°C (103.2°F) and pulse was 86. Rales were heard over the left side of the chest. A radiograph of the chest (Figure 1) showed left upper and lower lobe infiltrates. Abnormal laboratory values included a leukocyte count of 21,600 per cu mm with 14 percent band forms, a serum sodium concentration of 128 mEq per liter, an alkaline phosphatase value of 316 IU per liter, a lactic dehydrogenase (LDH) value of 462 IU per liter and a serum glutamic oxaloacetic transaminase (SGOT) level of 75 IU per liter. She was given erythromycin by mouth; there was prompt response. A convalescent titer for Legionnaires' disease was 1:512. Although she was oriented and alert throughout the admission, after discharge she said she had no memory of the details of her acute illness.

CASE 2. An 81-year-old man with adult onset diabetes was admitted to the Wadsworth Veterans Administration hospital for convalescent care following removal of an infected hip prosthesis in May 1977. In February 1978 anorexia, fever, recurrent shaking chills and a dry cough developed. Initially he appeared well, but over the next several days he became diaphoretic and confused. On physical examination on the fourth day of illness, he had a temperature of 39.9°C (103.8°F) with a pulse of 84. Examination of the chest disclosed findings of consolidation of the left lower lobe. The radiograph of the chest is seen in Figure 2. A transtracheal aspirate was done; occasional polymorphonuclear leukocytes and no organisms were seen on the Gram stain. There was prompt response to erythromycin therapy. Diagnostic seroconversion for Legionnaires' disease (from less than 1:64 to 1:512) was documented.

CASE 3. In a 55-year-old man with coronary artery disease (status after aortocoronary bypass) and adenocarcinoma of the prostate, malaise and

*Smoking histories are expressed in pack-years, which are computed by multiplying the number of packs of cigarettes smoked per day by the number of years in which the person has smoked.

nausea developed five days after admission. On the following day watery diarrhea, dry cough, shaking chills, fever and diaphoresis developed. The cough became productive of small amounts of blood and he complained of severe pleuritic pain. On physical examination on the third day of illness, the patient was dyspneic and diaphoretic; he was splinting because of chest pain. His temperature was 40.5°C (105°F) with a pulse of 130. Rales were heard bilaterally. Radiograph of the chest (Figure 3) showed bilateral infiltrates. Clinical improvement was noted within 36 hours of institution of intravenous administration of erythromycin. He became afebrile on the seventh day of therapy. Legionnaires' disease titers were less than 1:64 and 1:256 on the 3rd and 14th days of illness, respectively.

Diagnosis

There are three potential methods for diagnosing Legionnaires' disease: culture, showing the organism in tissue, and serology. The agent of Legionnaires' disease is a fastidious pleomorphic Gram-negative organism which has been cultured only rarely from clinical specimens. Investigators are attempting to develop artificial media which will routinely support growth of the organism, and specific recommendations have been made by the Center for Disease Control.[6] When the disease is suspected and special media are not available, the specimen should be inoculated on commercially available chocolate agar and incubated in 5 percent carbon dioxide atmosphere. A large inoculum should be placed in one quadrant of the plate, without streaking for isolation. A second inoculum should be streaked for isolation. The remainder of the specimen may be stored at −70°C for future processing.

There are at present four accepted methods of showing the presence of the agent of Legionnaires' disease in tissue or tissue exudates. These are Gram stain, Gimenez stain, Dieterle stain and the direct fluorescent antibody technique.[7,8] Of these, the Gram stain is the least reliable; the organism typically stains poorly or not at all in clinical specimens. The Gimenez stain appears to stain the organism reproducibly, and can easily be done on tissue exudates and frozen or formalinized tissue. Clinical experience with the Gimenez stain is too limited to comment on its potential value in Legionnaires' disease. The Dieterle silver impregnation stain, a stain heretofore used primarily for showing the presence of spirochetes, is an excellent tissue stain for Legionnaires' disease. However, this is a time-consuming stain which can only be done on formalinized tissue. It is important to be aware that the methenamine silver stain, a stain done routinely on lung biopsy specimens, does not stain the agent of Legionnaires' disease.

The best method for showing the organism is the direct fluorescent antibody technique. This is highly specific and can be done rapidly on pleural fluid, sputum, or tissue. The reagents for this procedure are not yet generally available; however, unstained slides or tissue sections may be sent to the Center for Disease Control, or to reference laboratories, for direct fluorescent antibody staining.

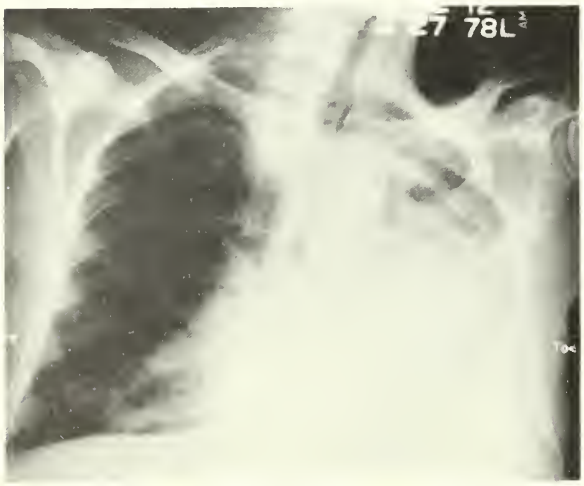

Figure 2.—Consolidation of the left lower lobe and bilateral pleural effusions in an 81-year-old man (case 2).

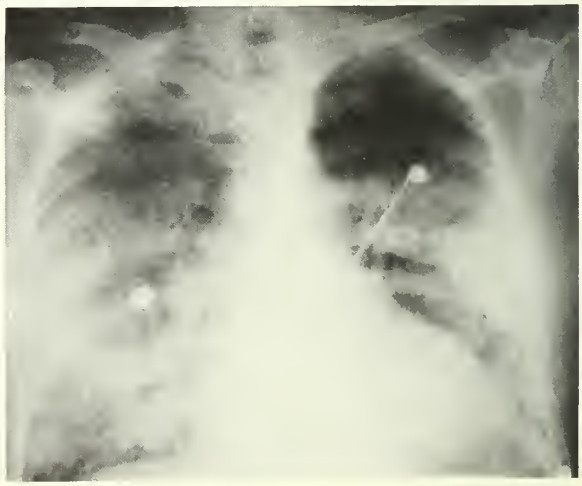

Figure 3.—Bilateral infiltrates in a 55-year-old man (case 3).

The third method of diagnosis, and the most practical, is by serology. The serologic test is an indirect fluorescent antibody test.

The current criteria established by the Center for Disease Control for the diagnosis of recent infection with the agent of Legionnaires' disease are either (1) a fourfold rise in titer to a level of 1:128 or greater or (2) a convalescent titer of 1:256 or greater in a patient with a compatible clinical illness. We obtained weekly titers on patients with Legionnaires' disease and determined that diagnostic seroconversion occurs in 64 percent by the end of three weeks, in 82 percent by the end of four weeks and in all patients by the end of six weeks.[3] Therefore, it is important for physicians to obtain a serum specimen at the onset of illness and to follow this with specimens obtained weekly or biweekly for up to six weeks.

Therapy

The drug of choice for the treatment of Legionnaires' disease is erythromycin.[3,6] The selection of erythromycin is based on (1) a decreased case-fatality rate in the Philadelphia outbreak in patients treated with erythromycin or tetracyline and (2) protection studies done with erythromycin and other antibiotics in guinea pigs and embryonated hens' eggs.[1,9] Although *in vitro* antibiotic susceptibility testing suggests that the organism is susceptible to most antibiotics, the clinical experience has been that Legionnaires' disease clearly progresses in patients treated with penicillins, cephalosporins, aminoglycosides and clindamycin. Tetracycline and rifampin may be alternative agents; however, because of the problem of rapid development of resistance to rifampin of other organisms during therapy, it is unlikely that rifampin will be recommended as a single agent.

The response to erythromycin therapy is prompt and dramatic. The patient typically begins to look and feel better within 24 hours after institution of therapy. The temperature often does not return to normal for several days; however, a trend toward normal is usually apparent within 24 to 48 hours. The dose of erythromycin is 500 mg, given by mouth or by vein, every six hours for three weeks. Courses of therapy of two weeks or less may be associated with relapse or with protracted convalescence, whereas patients treated for three weeks uniformly do well.

In conclusion, Legionnaires' disease is a newly recognized, albeit not new, disease. Over the next few years, its spectrum, prevalence and epidemiologic importance as a cause of bacterial pneumonia in humans will undoubtedly be more clearly defined.

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Important Advances in Clinical Medicine

Epitomes of Progress—Psychiatry

The Scientific Board of the California Medical Association presents the following inventory of items of progress in psychiatry. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in psychiatry which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Psychiatry of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Biofeedback in Psychiatric Practice

BIOFEEDBACK refers to various methods for providing a person with rapid information (feedback) about one or more of his or her biological systems. The usual purpose of such biofeedback is to allow the person to gain conscious control over those biological systems. For example, electromyograms can be used to provide an indication of muscle tension and can help in learning to relax or to strengthen the muscles. Biofeedback-aided relaxation has been used to relieve tension headaches, and biofeedback-aided exercise has been used to restore functioning of atrophied muscles.

Modern technology can now provide biofeedback of many functions, including skin temperature, muscle tension, brain waves, blood pressure, pulse rate and galvanic skin response. Rapidly, perhaps too rapidly, biofeedback has been advocated for an increasing list of conditions: (1) epilepsy, (2) muscle problems such as atrophy, tension, bruxism and tension headaches, (3) cardiovascular conditions such as hypertension, pulse irregularities, Raynaud disease and migraine headaches and (4) a variety of ills such as alcoholism, asthma, chronic anxiety, diabetes, sexual impotence and diverse psychiatric syndromes. Philosophically, biofeedback research provides important insights into the extent to which conscious control can be exercised over automatic body functions. Practically, it offers the promise of allowing the sufferer to take responsibility for correcting his own faulty body processes.

Biofeedback is indeed a technique with clinical promise, but it has often been overenthusiastically advocated before clinical effectiveness has been carefully shown. It is definitely indicated for bruxism, subvocalization and tension headaches. A very specialized electroencephalographic feedback has proved effective in certain cases of epilepsy. Many of the other uses are still experimental and await adequate clinical evaluation.

JOE YAMAMOTO, MD
ENOCH CALLAWAY, MD

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New Methods in the Treatment of Chronic Pain States

THERE HAVE BEEN advances in the treatment of chronic pain in three fields: electrical, chemical and behavioral.

Transcutaneous electrical neurostimulation is a benign, noninvasive analgesic technique which is effective in a variety of pain states such as causalgia and other reflex sympathetic dystrophies, postherpetic neuralgia, low back pain and sciatica, degenerative disease of the spine, diabetic and alcoholic peripheral neuropathies, and similar chronic pain conditions. Neurostimulators are small battery-operated pulse generators with electrodes which can be taped in the distribution of the pain, and which can be worn continuously. Originally, it was thought these devices worked by stimulating large sensory fibers and thereby "closing the gate" in the dorsal horn of the spinal cord to noxious stimuli transmitted in thin myelinated and unmyelinated fibers. Recent studies have shown the effect is largely a direct "fatiguing" of the peripheral small pain fibers, but whether it is by depolarization or hyperpolarization is not yet clear. Some central inhibiting effect probably also occurs, however, because peripheral stimulation is also effective in cases of thalamic pain.

Neurophysiological studies have shown that the periaqueductal gray area of the caudal mesencephalon, around the dorsal raphe nucleus, is involved in pain suppression; its stimulation produces a profound peripheral and visceral analgesia. This area is also rich in opiate receptors, and in serotonergic neurons. Depletion of brain serotonin leads to decreased pain tolerance; administration of serotonin precursors restores pain tolerance to normal levels. This suggests that the common reactive depression seen in patients with chronic pain may be an effect of disturbed brain serotonin activity, perhaps due to continued noxious input or chronic narcotic use, or both. It also provides a rationale for the empirical finding that tricyclics with more specific effect in blocking the re-uptake of brain serotonin than brain norepinephrine, such as amitriptyline and doxepin as compared with protriptyline and desipramine, seem more effective in managing patients with chronic pain. Patients given 75 mg to 150 mg of amitriptyline every night reported sleep patterns and a subjective sense of being better able to tolerate their pain.

Patients with chronic pain have responded favorably to operant conditioning techniques directed at specific pain behaviors. Inpatient programs using such methods have shown increased activity levels, decreased pain levels and decreased analgesic intake, and these gains have been maintained on follow-up. Another version of this condition, biofeedback training, is particularly effective when directed at physiological processes underlying pain symptoms: muscle training for muscle spasms and muscle contraction headaches, vascular flow for certain vascular headaches and Raynaud phenomena, and the like.

The combination of electrical, chemical and behavioral methods is providing a significant degree of pain relief in 65 percent to 70 percent of patients who just a few years ago could not be helped.

RICHARD A. STERNBACH, PhD

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Alcoholic Adolescents

COMPARED WITH THE 1960's, the 1970's have shown an increased use and abuse of alcohol by teenagers. This has coincided with a decrease in the use of "hard" drugs, such as LSD, amphetamines and barbiturates, while being paralleled by an increase in the use of marijuana. The trend was first noted on college campuses, and is now shifting into high schools.

Most studies indicate that most teenagers will have experimented with alcohol before graduation from high school. However, there is a pronounced difference between those who use alcohol occasionally and those who become alcohol abusers. There are at least four major factors which differentiate adolescent problem drinkers from those who occasionally use alcohol: the presence of an alcoholic parent, unmet psychological needs (particularly the need to be cared for), delinquent behavior patterns and peer-group abuse of alcohol.

Once started down the path of alcohol abuse, adolescent problem drinkers are prone to a wide variety of other problems. Suicide attempts are

much higher in this group. Of younger alcohol abusers surveyed, 45 percent had attempted suicide at least once. Most authorities agree that a higher incidence of abuse exists among juvenile delinquents. While the exact figures are not known, many of these users will go on to become alcoholic adults, while some will have normal drinking patterns in later years.

Treatment depends on prompt recognition and the institution of an appropriate regimen. Recognition can be a problem. The public in general does not readily acknowledge alcohol abuse in young people. Similarly, most young alcohol abusers seem loathe to accept the fact that they have a problem with alcohol. However, proper education of both the medical profession and the public to the fact that this entity does exist can overcome some of these resistances toward early recognition.

JULIAN KIVOWITZ, MD

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Stimulants and Hyperkinesis

HYPERKINETIC CHILDREN have received the most attention in recent years as recipients of stimulant drugs. Some estimate that at least 300,000 children in elementary schools are receiving psychotropic medication for school difficulties and that 3 percent to 8 percent of elementary school children are hyperkinetic. Yet fewer than 25 percent of hyperkinetic children are treated with medication.

The term hyperactive (or hyperkinetic) has come to be associated with, to stand for or to be synonymous with such diverse terms as minor or minimal organic brain dysfunction, damage or disease; hyperkinetic impulse disorder; behavior syndrome or cerebral dysfunction, and about 30 others. There are many causes of hyperactivity in children and stimulant drugs are useful only in some of them. Hyperactivity is a symptom that describes behavior and can occur in any psychiatric disorder in children. It can occur in psychotic reactions, in psychosis associated with organic brain syndromes, in behavior disorders of childhood and even in transient situational disturbances. Learning disorders occur with all diagnoses and with no mental disorder, and some children with the hyperkinetic reaction behavior disorder of childhood have no cognitive disturbance. The minimal brain dysfunction syndrome should be limited to children who show some minor sign of cerebral dysfunction which could include any one of specific patterns of motor, perceptual or cognitive disturbance.

Drug treatment must be a part of the total program for a child and consideration must be given to complementary therapy methods—work with families, suitable programs for the child, educational planning, special groups and psychotherapy. Good medical care requires a thorough diagnostic evaluation of the psychiatric, neurologic, psychological and educational impairments, followed by an adequate trial of appropriate remedial education and a careful evaluation of which drug is most hepful.

Drugs should not merely provide a relatively easy and economical way of making the classroom situation more tolerable and manageable for teachers. Medication is recommended when a child with remedial and psychological help continues (even when out of a stressful situation) to show attention difficulty that significantly interferes with his academic or social functioning.

Methylphenidate and dextroamphetamine are effective in only 60 percent to 70 percent of behaviorally defined hyperactive children. They produce a decrease in hyperactivity and impulsiveness and an increase in attention span. There is a difference of opinion as to the effectiveness of the two drugs used. Methylphenidate recently has been preferred in dosages of 0.5 mg per kg of body weight twice a day, although at present it is recommended that on initiating therapy one dose of medication a day should be given and a second dose given only if necessary. Dextroamphetamine has often been effective in dosages of 2.25 mg per kg of body weight and may also be given as a long-lasting capsule. There are large individual differences in blood levels in children of the same body weight for comparable doses of the same drug. Prospective and retrospective follow-up studies show that children may become less active, impulsive and excitable by the time they reach adolescence, but continue to be more restless and aggressive than controls matched

for age and sex. A substantial minority may have psychiatric and social problems in adolescent and later life.

The long-term use of dextroamphetamine in hyperactive children causes a highly significant suppression of growth in weight and height. Tolerances develop to its weight suppressant effects but not in inhibition to height growth. The long-term use of methylphenidate causes a less striking growth suppression only when daily doses over 20 mg are administered. In a follow-up study of adolescents who had received methylphenidate in childhood for minimal brain dysfunction there was no serious interference with growth and height.

Reports conclude that with proper supervision there is a place for the use of drugs as one of the therapeutic methods in treating hyperactive children, but that the possibility of unforeseen long-term consequences indicates caution.

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The Use of Phenothiazines in Children

CHLORPROMAZINE was the first and initially most widely utilized phenothiazine in child psychopharmacology and has been used primarily for psychosis for more than 20 years. Thioridazine has also been a widely used drug. Indications for its use are agitation; hallucinations and delusions; hyperactivity; anxiety; terror and hostility when these are symptoms of psychotic illness; mental retardation, or organic brain damage.

Both drugs are widely used in the treatment of autistic children but because of their sedative effects they might be contraindicated for long-term administration because they seem to have a negative effect on cognitive behavior and learning. They have been of value for school-age schizophrenic children with acute as well as chronic symptomatology but have caused sleepiness and psychomotor retardation even in low doses.

Fluphenazine is highly effective in prepubertal autistic schizophrenic children, and trifluoperazine has proven to be somewhat better than chlorpromazine in autistic children. Ideally, drugs should enhance learning and should not be used as chemical straitjackets for psychotic retarded children. Drowsiness and lethargy are the most common side effects. Abrupt drug withdrawal of psychotropic drugs causes neurologic withdrawal emergent symptoms most of which involve involuntary movements in the trunk, head and ataxia.

ROBERT A. SOLOW, MD

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Drug Treatment of Affective Illness in Children

THE CONCEPT of depression in young children has not yet found wide acceptance in the United States as it has in other countries. Drugs which have been shown to be effective antidepressants in adults have not been as well evaluated in depressed children, particularly those with psychomotor retardation. The symptoms of irritability, excessive crying, fretfulness and pronounced insomnia are useful criteria for the recognition of endogenous depression in children one to three years old. This condition and a variety of disorders in older children in which depression dominated the clinical features have been treated with tricyclic antidepressants. Depressed children have shown impressive evidence of hyperactivity, enuresis and temper tantrums in addition to the symptoms characteristic of depression. It has been observed that the greater the hyperkinesia and hyperactivity, the more positive were the effects obtained from the use of tricyclic antidepressants. Imipramine has been administered starting with 10 mg and increasing by 10 mg every third day until improvement was noted: 300 mg being the maximum dose given. Childhood manic-depressive illness and cyclic alterations of mood that are at a level of clinical significance have been treated with lithium carbonate

as have conditions characterized by rapid shifts in mood, overactivity and restlessness. Lithium is believed to be a safe drug for investigation in children but is inadequate for treating hyperactivity unresponsive to stimulant medication.

ROBERT A. SOLOW, MD

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Cerebral Lateral Asymmetry and Psychiatric Issues

THE TWO CEREBRAL HEMISPHERES exhibit cognitive specialization and the potential for independent functioning. This provides a useful conceptual framework for relating styles of thinking, psychological defenses and variations in awareness.

Observations on split-brain patients indicate that each disconnected hemisphere is independently conscious and that, in general, the left hemisphere dominates their postoperative behavior. A parallel is noted between the functioning of the isolated right hemiphere and mental processes which are repressed, unconscious and unable to directly control behavior. Both the right hemisphere cognitive mode and primary process thinking are characterized by image representations, nonsyllogistic logic and little concern for temporal sequencing. Perhaps even with an intact corpus callosum, mental events in the right hemisphere can become disconnected functionally from the left hemisphere (by inhibition of neuronal transmission across the corpus callosum) and can continue a life of their own. This suggests a neurophysiological mechanism for at least some instances of repression and indicates an anatomical locus for unconscious mental content.

If repression is subserved by a functional disconnection of right hemisphere mental processes, unconscious ideation would be expressed primarily through channels not preempted by the dominant verbal left hemisphere. Several studies suggest that the right hemisphere does play a special role in dreaming and in conversion symptoms and other psychosomatic disorders.

The two hemispheres also show differences in affective reactions or coping strategies following unilateral cerebral injuries or in the course of the intracarotid amytal test. Denial of illness or euphoria is seen most often following right lesions and "catastrophic" or depressive reactions most often following left lesions.

DAVID GALIN, MD

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Life Stress and Disease

PEOPLE have long known that life stress is in some way correlated with the onset and course of illnesses. This knowledge, however, was always in the form of anecdotal evidence only. Beginning some years ago investigators pioneered a method of quantifying life stresses.

Because almost every person has had experience with marriage in one context or another (either as a marriage partner or as a member of a family), and therefore has an opinion of its meaning in his life, marriage was used as a yardstick of the effect of life changes on a person's adjustment pattern. For research purposes, marriage was given an arbitrary weight of 50 points. Various populations were then asked about the disruptive effect on their lives of other life events as they compared with marriage. Examples of such life events are getting divorced, being fired from work, getting promoted or having a spouse die. Each was given a certain number of points based on marriage as 50. This system allowed for subjects' recent life stresses to be represented numerically, with stress totals determined for arbitrary time intervals—such as one year. The hypothesis was that persons with high life stress scores would be more likely to become sick than persons with low life stress scores.

Numerous studies, both here and abroad, of a retrospective as well as prospective nature have amply confirmed the hypothesis. Persons with a high life stress score are indeed much more at risk than those with low scores. In addition, the higher the score, the more likely that the illness that develops will be a serious one. These relalationships are actuarial rather than absolute in character, so that not everyone with a high score gets sick, but the tendency is definitely present in groups of such persons.

The body is continuously subject to all kinds of environmental assaults on its integrity. There have to be changes in the body's defense mechanisms for a clinical illness to occur. Psychosocial events can have a profound effect on the internal milieu of the body. These effects are mediated through the neuroendocrine systems and the neuro-control of such other body systems as the cardiovascular and the pulmonary. Any persons with a recent accumulation of many (or a few very severe) life changes should make every effort to live as hygienically as possible in an attempt to prevent disease outbreak.

RANSOM J. ARTHUR, MD

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Early Identification of Psychiatric Problems and Early Intervention

SECONDARY PREVENTION depends on two processes: first, the early identification of psychiatric problems and then the prompt intervention to minimize the effects of the disorder on the child and family.

Early Case Finding

As is always true in child mental health, early identification is best approached from the developmental standpoint. Initial concern is directed toward the identification of problems in the premature infant. Programs have been developed which utilize both specialized nursing care and the involvement of parents with the child within the first few days after birth. There are approaches designed to provide stimulation both to infant and mother, methods which give the person handling the baby special opportunities for handling and feeding in a setting which is conducive to being at ease and relaxed.

The First Year of Life

During the first year of life, the opportunities for early identification and intervention are highly dependent upon the precise observations of health and mental health personnel who come in contact with the child and mother. It is now possible to document the fact that, for whatever reasons, a given mother and her child seem to be having difficulties.

A number of studies have been reported describing early intervention in the first year of life. There are data showing effective intervention can be accomplished by working with mother-infant pairs and with groups of mothers and infants with similar but not the same problems. Groups in which mothers can share with other mothers who have similar concerns and worries are an effective means of education.

An infant's failure to gain weight and to thrive are early signs of difficulties which need attention. Both the infant and the parents require help from mental health and health specialists.

Preschool and Primary School Years

In the preschool years, especially in various nursery schools and Head Start programs, there are opportunities to observe children and to detect a variety of difficulties. Behavior such as overactivity, extreme clumsiness, anxiousness, incapacity to separate from mother, severe isolation, and failure to develop speech and other developmental landmarks may be signals of neurophysiological or psychological disturbance. In most instances, they are symptoms indicating a need for early intervention through work with both the child and parents.

There is some evidence that by the time a child enters school many patterns of adaptation and social behavior have been established which will be difficult to change. There is, however, much to suggest that early identification of children who have learning problems will raise the question to be explored that they are at risk and vulnerable in the school setting. Bateman and her group have estimated that 15 percent to 20 percent of school children have fairly severe learning problems; most of these are primarily evident as behavior difficulties in school.

The role of chronic disease during this period is especially important. The identification of chronic disease frequently occurs during the school years and often greatly interferes with the learning and socialization processes.

Secondary Prevention in Adolescence

In discussing issues of secondary prevention in adolescence, there are a number of issues to keep in mind. One is the increasing number of adolescent suicides. Another is the rise in the number of adolescents in whom psychotic, especially schizophrenic, disorders develop. Still another is

the fact that psychosomatic disorders such as anorexia nervosa are primarily diseases of adolescence. Similarly, one of the critical issues in young adolescents, especially for young women but of great importance to young men as well, is unwanted pregnancy. For many young women who have not had previous experiences in closeness and nurturance, sexual maturity and sexual attractiveness may mean sexual involvement as a means of feeling wanted, close to another person and loved. Recent efforts have been made to involve young pregnant unmarried women in continued education. They have been given classes in child development and they have been taught in nursery schools attached to the schools about being parents.

Crime, delinquency and homicide are appallingly high in adolescence, especially among the black and the poor. Many of the issues which center around these problems are related to the socioeconomic conditions in which these youths develop.

The early detection of psychiatric disorder in early childhood (as well as later) depends upon how well health and mental health professionals can educate parents. The translation of observations must be made in terms of the effects both of intrapsychic stress and environmental stress on the adaptive functioning of young infants, children and adolescents.

IRVING N. BERLIN, MD

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Loma Linda University

THOMAS A. GONDA, MD
Stanford University

E. MANSELL PATTISON, MD
University of California, Irvine

LOUIS J. WEST, MD
University of California, Los Angeles

LEWIS JUDD, MD
University of California, San Diego

LEON EPSTEIN, MD
University of California
San Francisco

P. R. SLAWSON, MD
University of California, Los Angeles
President
California Psychiatric Association

EDITORIALS

Elective Operations and the Death Rate

At a recent meeting of the American Public Health Association Dr. Milton L. Roemer reportedly noted that there was a significant drop in the death rate in Los Angeles County in early 1976 when many doctors withheld their services to protest rising malpractice insurance premiums. Dr. Roemer is said to have attributed the lower death rate to the sharply reduced amount of elective surgical procedures that occurred during the slowdown. The *Washington Post* then reportedly quoted Dr. Roemer as saying that the lower death rate lends support to "the mounting evidence that people might benefit if less elective surgery were performed in the United States" and that greater restraint in carrying out elective surgical operations might well improve life expectancy. All of this has received considerable publicity.

It is not the intention here to question the data and it is even possible that the interpretation attributed to Dr. Roemer may be correct. But if so, the interpretation (1) assumes that the operations postponed and therefore not done during this period were elective in the sense that they might not need to be done at all and (2) implies that elective operations on the whole do more harm than good. For the first it seems obvious that many necessary, serious and even risky operations or procedures can safely be postponed until conditions are optimal to undertake them. This is often done and seems more than likely to have occurred in many instances during the trying period early in 1976 in Los Angeles when many would have considered conditions for nonemergency operations less than optimal. For the second it would seem reasonable to consider the benefits for which the risks were or would have been taken had these "elective" operations been done. This point does not seem to have been addressed. But again, it seems likely that in many and possibly most of these instances, there would have been benefits which in the opinion of the doctor with the informed consent of the patient would have been worth the risk of operation to the patient. Coronary bypass and inguinal herniorrhaphy are two surgical procedures which are ordinarily not considered emergencies but neither are they in the same elective category as rhinoplasty for cosmetic purposes, for example. But even in this instance it may be well worth it to the patient. Certainly in the appropriate instances and at the appropriate times it is good medical practice to do these operations and to assume the risks to achieve the benefits for the patients.

It is becoming evident that the costs, risks and benefits of various physician interventions in patient care will be undergoing increasing study and scrutiny. It is most important that when this is done, these risks, benefits and costs be accurately assessed in relationship to one another as each physician intervention is studied.

—MSMW

Physical Child Abuse

The current issue of this journal carries a report from the Sacramento Medical Center on the initial findings and short-term outcome of cases of physical child abuse, diagnosed and reported during the calendar year 1975. This is welcome feedback to the medical profession on some of the reports initiated by physicians, a feedback lacking in most communities. During the past 15 years the problem of child abuse has been highlighted both in lay and professional literature. All 50 states have enacted laws requiring physicians and many other professionals to report suspected child abuse. Vice President Mondale, while he was still in the Senate, was instrumental in establishing a National Center for Child Abuse and Neglect responsible for conducting educational and demonstration research programs in the field of child abuse. Each federal district has a regional child abuse project and the state of California now has an Office of Child Abuse Prevention. These are all positive steps and one would expect them to improve the quality of life for abused children and their families, and to avert some abuse in the future. Prevention of child abuse before it occurs is an even more important goal of these programs. However, the true extent to which such improvement has oc-

curred is not at all clear, and still remains to be documented. In the meantime the current mood of many state legislatures is to stress reporting and impose increased penalties for failure to report child abuse. Among the recently enacted statutes is one requiring that all medical students receive instruction in child abuse before they can be granted an MD degree; one requiring mandatory continued instruction in the field of child abuse for physicians as a condition for relicensing, and one which would significantly increase penalties for failure to report abuse. Many other proposed bills would change various aspects of reporting and registries for child abuse cases. In addition, new written forms for reporting have been prepared recently by the state Attorney General and compliance with the new forms will probably be requested in the near future.

We heartily endorse the current reporting laws as a *beginning step* in protecting children at risk and assisting family units in handling crisis situations. No doubt the present laws could be improved, particularly by clarifying the statute, but the important fact is that reporting child abuse for the sake of compiling statistics has no redeeming value.

Physicians are motivated to report child abuse in order to protect the patient from further harm, to be law abiding and because of their awareness that failure to report may carry some civil liability if the child should come to further harm.

On the other hand the medical community should insist that such a report lead to prompt intervention designed to protect the child. This is a challenging task but the framework for successful intervention has been nicely delineated.[1] Removing a child from a family to long-term, sometimes open-ended foster care is not in the best interest of the family or the child; and is very expensive for society. The diagnosis of child abuse should result in prompt, humane intervention, perhaps a short period of separation, and organized coordinated support for families permitting the safe return of the child into the home. An alternative for a minority of instances is termination of parental rights leading to early adoption or legal guardianship when it is clear that family reunification cannot be achieved. The California Legislature has recently authorized a four-year trial of an innovative plan of this type in three counties in the state. We would like to emphasize that there is ample evidence that the child, as well as the family, needs special support and treatment.[2] Physicians, who so often initiate the child abuse report, need to join with other professionals and parent groups, participate in community child abuse councils and work towards the realization of these goals.

The present retrenchment of local tax revenues makes it particularly timely and urgent that we emphasize these expectations and that we continue to receive feedback on the events that follow the reporting of child abuse cases. Yes, we as medical professionals assume the obligation for reporting child abuse and will be accountable for failing to do so. It is only fair that we should expect the agencies that receive our reports to be equally accountable for the actions and outcomes that follow. Such outcome studies and reports are essential in order to judge the effectiveness of the statutes, programs and fund expenditures. We hope to see more of them in the future on the pages of this and other journals.

MOSES GROSSMAN, MD
Professor of Pediatrics
University of California, San Francisco
Chief of Pediatric Services
San Francisco General Hospital

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On Assuring Health Through Health Care

ON THE FACE OF IT, it sounds logical enough to assure health for all by making health care available to all and persuading everyone to take advantage of it. This has been a widely accepted thesis for some years and it has been one upon which much health planning and many costly initiatives of government have been based. Now it appears that as more health care becomes available to more people who use more if it, health does not improve proportionately to the effort and dollars expended. It would seem that there must be some kind of fallacy in this thesis or assumption which has seemed so logical to so many.

It is suggested that an explanation may lie in the almost casual substitution of the word-symbol "health" for the word-symbols that mean illness, injury or sickness of whatever kind. It appears to have started when medical insurance was designated health insurance, and when medical care

by common usage became called health care. All of this seems innocent enough on the surface, but word-symbols are important. We use them to think and to express our thoughts, and they are important in the development of ideas, concepts, attitudes and beliefs. Words must be used accurately with respect to their meanings, or thought; when words are used inaccurately, ideas, concepts, attitudes and beliefs can become distorted and lead to unintended and usually unrecognized irrationality. There are some of us who believe this may be what has happened as health care has gradually replaced medical care in both professional and public parlance.

This subtle substitution of the health word-symbol for sickness word-symbols appears now to have produced costly confusion as to who is responsible for what in health and the mistaken assumption or belief that medical services provided by health insurance can somehow be expected to assure health. The evidence for this is to be found in the government's loudly proclaimed emphasis on the prevention of illness and maintenance of health through medical services available through health insurance or otherwise, and the related public castigation of the medical profession because it succeeds so poorly in keeping the public well.

It seems likely that much of the confusion and no little of the expense in medical and health care stems from this arbitrary displacement of a word symbolism which to be sure connotes unpleasantness and discomfort with one which implies well-being and vitality. The expensive confusion which seems to be the unfortunate result of this innocent symbol substitution will not be easily sorted out, for we all think with symbols which come to have meanings for each of us, though not always the same meanings for all of us. But sorted out it should be, for the primary function of medical care (now known by common usage as health care) is to diagnose and treat the sick, injured and emotionally disturbed, and seek to restore them to as much health and quality of life as is possible. Yet physicians and the medical profession have a duty to contribute their knowledge and expertise to health for individual persons and the public. The preventive measures medicine can offer are important but limited. The assurance of health is actually largely the responsibility of all well persons themselves and of society as a whole, although physicians can and should be well-informed advisors. But neither health insurance nor health care can assure health and any thesis or assumption to the contrary is illusory and needs to be exposed for what it is whenever and wherever it appears.

—MSMW

Hidden Spinal Malformations

When clinicians refer to a disorder as hidden or occult they seldom pause to consider that most of the ills of man are in a sense hidden—beneath the surface. The important components of those malformations that affect the spine are more often hidden than apparent: spina bifida occulta is more common than spina bifida apperta. Yet there are always clues to that which is hidden. The extraordinary increase in our experience of spinal dysraphism in the last 15 years bears witness to the spreading awareness of those syndromes especially among pediatricians, orthopedic surgeons and urologists. When considering the causes of lower limb asymmetry or weakness or urinary incontinence or repeated urinary infections, it is only necessary to examine the skin on the back carefully to determine whether the next stage of investigation should be radiography of the spine. This is because *both* the principal derivatives of ectoderm—the skin and the central nervous system—are likely to be affected by those influences which cause malformations. The mesodermal element, the skeleton, will inevitably be affected too —hence the need for radiography. Whether to investigate further and how to do so are questions not settled among those with experience of these disorders.

It is well to remember that in many cases the lower limb abnormality or sphincter disturbance is present at birth and should be regarded as an associated abnormality rather than resulting from cord malformation. When there is evidence of *progressive* neural loss, there can be no question that an attempt must be made to arrest that progress. When the cord is partially immobilized by a short thick filum or fibrous band or dermal sinus or a structure running between the half cords of diastematomyelia, mobilization by spinal exploration is certainly effective. The complex lipoma, however, may intermittently involve cord and nerve roots so that dissection must carry the risk of damage and may fail to achieve complete freedom of the neural structures. Before such

surgical intervention, most neurosurgeons require a clear delineation of the structures and the spinal canal, which means myelography. Air has been the most favored contrast medium but is being rapidly superseded by metrizamide.

The recognition of spinal dysraphism (perhaps miscalled occult or hidden, except by those who do not realize the significance of the stigmata) is often possible in children who have no lower limb or urinary troubles. Confirmation of probable cord malformation by plain spinal radiography then poses the question whether myelography should be carried out. What happened to all those children whose dysraphism was overlooked years ago? Probably only a small proportion suffered progressive neural damage. Yet it is very likely that early operation can reduce this risk to nearly nil.[1] To await muscle weakness or sphincter disturbance—both difficult to detect in the early stages in a young child—is to allow an irreversible disability to develop. The question of preventative or prophylatic surgical operation is unresolved. I think, however, that we can more readily accept that operation is justified in those otherwise normal children who have certain types of dysraphism such as diastematomyelia with the cord closely applied to the bony spur, or a cord greatly immobilized by bands or attached to the dura.

There is one important aspect of spinal dysraphism where there can be no controversy and where we may be grateful for the information derived from a study of a large number of these children. The suspicion that these conditions were genetically related to neural tube malformations—spina bifida cystica and anencephaly—is now well proven.[2] A study of the families of 207 patients with spinal dysraphism showed that the mothers were as likely to produce siblings with these lethal or gravely disabling conditions as were those mothers who already had given birth to a baby with anencephaly or spina bifida cystica. It follows that such mothers should be offered prenatal screening for neural tube malformation by alpha fetoprotein estimation in blood or amniotic fluid. The parents with children with spinal dysraphism should therefore be informed of these possibilities. Here lies a fresh incentive to detect those children with spinal dysraphism even if the condition is not thought to require operation.

KENNETH TILL, FRCS
Consultant Neurosurgeon
The Hospital for Sick Children
London

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A Brain Drain to Elsewhere?

THE NEWS that some American research scientists are beginning to find government restrictions and red tape so difficult or impossible that they are beginning to do their research abroad is disquieting. It suggests the possible start of something like a reverse brain drain which, if it occurs, could only be to the long-term disadvantage of this country. At the moment it is the promising and urgent research in recombinant DNA that is at particular issue, but the larger question is whether or not we will sooner or later regulate ourselves out of the running in scientific research as we appear to be doing in some segments of the faltering economy.

It was not too long ago that medicine in this nation benefited greatly from the immigration of many well-trained physicians and medical scientists from Great Britain. It will be recalled that they came to this country because of their dissatisfaction and frustration with insensitive governmental regulation and red tape in the National Health Service of that country. This exodus of physicians to the United States of America was considerable and was referred to on both sides of the Atlantic as the "brain drain." Its effects on the physician manpower of both nations remain to this day.

Politicians, like many other humans, tend to become uncertain and sometimes even to panic when faced with the unknown. This appears to be what has happened with our governmental approach to research with recombinant DNA. But mankind has not got where it is by running away from the unknown or trying to ignore it. Rather mankind has progressed by challenging the unknown and exploring it, even at some risk. The world is larger than the USA and the portents are that the research on recombinant DNA will be done elsewhere if not in America. A brain drain to elsewhere seems a high price to pay for what can at best be only a temporary and false sense of national security.

—MSMW

CASE REPORTS

Refer to: Taetle R, Wohl H: Oat cell carcinoma mimicking acute leukemia. West J Med 129:497-500, Dec 1978

Oat Cell Carcinoma Mimicking Acute Leukemia

RAYMOND TAETLE, MD
HERBERT WOHL, MD
San Diego

THE CLASSICAL appearance of carcinoma metastatic to bone marrow has been known since the description of Kingsley-Pillers and co-workers.[1] In more recent years, this manifestation of carcinoma has been recognized with increasing frequency,[2,3] especially for oat cell carcinoma of the lung.[4,5] Despite the frequency of occurrence of marrow involvement, severe pancytopenia secondary to carcinoma remains an uncommon event associated with a poor prognosis.[7-9] We present a case of oat cell carcinoma metastatic to marrow accompanied by pancytopenia, which closely mimicked acute lymphoblastic leukemia.

Report of a Case

The patient was a 50-year-old white man first seen at the San Diego Veterans Administration Hospital in August 1976 with complaint of pain on the right side of the chest. At that time, physical examination, x-ray studies of chest and ribs showed no abnormalities, and the patient was discharged on a regimen of oral analgesics. He returned November 1, 1976, complaining of persistent pain on the right side of the chest. Physical examination again showed nothing remarkable except for a fever of 38.5°C (100°F) orally. An x-ray study of the chest now showed a right upper lobe infiltrate and right peritracheal and left hilar masses. Cytological examination of sputum specimens gave positive results for oat cell carcinoma. Results of routine chemistry determinations and complete blood count were normal with the exception of a leukocyte count of 11,700 per cu mm, with a normal differential. Eight to ten platelets were present per high-power field on a routine peripheral blood smear. Smears of a bone marrow aspirate from the right posterior iliac crest showed rare clumps of tumor cells in several smears and the clot section. A right iliac crest needle biopsy specimen showed no evidence of tumor.

Radiotherapy to the mediastinum and right supraclavicular areas was given for relief of pain, and the patient received 2,000 rads (200 rads per day in two weeks) to these areas. During the radiation therapy, the patient's fever abated in response to orally administered penicillin, and x-ray studies of the chest showed improvement; however, his general condition deteriorated. On November 19, 1976, combination chemotherapy was planned, and a pretreatment complete blood count showed a leukocyte count of 6,300 per cu mm; hematocrit, 43 percent; but platelet count of only 36,000 per cu mm. Results of tests for fibrin split products were negative. Because of the rapid supervention of the patient's thrombocytopenia, the possibility of a drug reaction was strongly considered. Administration of penicillin and isoniazid (INH®) was discontinued and a regimen of orally administered prednisone, 60 mg daily, was begun.

After three days of prednisone therapy, the leukocyte count was 5,200 per cu mm; hematocrit, 44 percent, and platelet count 7,600 per cu mm. A repeat right iliac crest bone marrow aspiration and biopsy was done. Smears of the bone marrow aspirate showed complete replacement of marrow elements with immature, "blast-like" cells with a high nuclear/cytoplasmic ratio, and vac-

From the Division of Hematology/Oncology, Department of Medicine, San Diego Veterans Administration Hospital and University of California, San Diego, School of Medicine.

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Reprint requests to: Raymond Taetle, MD, Division of Hematology/Oncology (111E), San Diego Veterans Administration Hospital, 3350 La Jolla Village Drive, San Diego, CA 92161.

uolated and intensely blue cytoplasm (Figure 1). No tendency of these cells to clump was noted. Special stains for periodic acid, Schiff; Sudan black, and peroxidase were negative. Because of the extensive and very rapid total replacement of normal marrow by these immature cells, the possibility of a hematologic malignancy was considered. Results of cytological studies of the patient's sputum were reviewed and were considered compatible with this possibility.

With the patient's informed consent, treatment with cyclophosphamide and vincristine was begun for his original diagnosis, despite his serious thrombocytopenia. Studies of a bone marrow biopsy specimen, available for review two days later, clearly showed normal areas of bone marrow being invaded by foreign cells consistent with oat cell carcinoma (Figure 2). The patient's subsequent course is summarized in Figure 3. The leukocyte count and hematocrit had also begun to fall before therapy, and the former was 3,000 per cu mm on day 1 of his first course of chemotherapy. Administration of prednisone was discontinued, and he received cyclophosphamide, 1.5 grams per sq meter, and vincristine, 2 mg intravenously. The platelet count reached a nadir of 5,000 per cu mm one day after treatment, and he received platelet transfusions. Subsequently the platelet count rose rapidly and he received no further platelet support. The leukocyte count reached a nadir of 835 per cu mm one week after administration of cyclophosphamide was started. He recovered completely from the effects of his pancytopenia and left the hospital with a leukocyte count of 6,000 per cu mm and a platelet count of 180,000 per cu mm. Two weeks after the second marrow aspiration, a third right iliac crest biopsy was done. Attempts at aspiration were unsuccessful, but the biopsy specimen showed extensive fibrosis without evidence of malignancy. Radiation therapy to the lumbar spine for relief of pain had been started two days before the bone marrow aspiration.

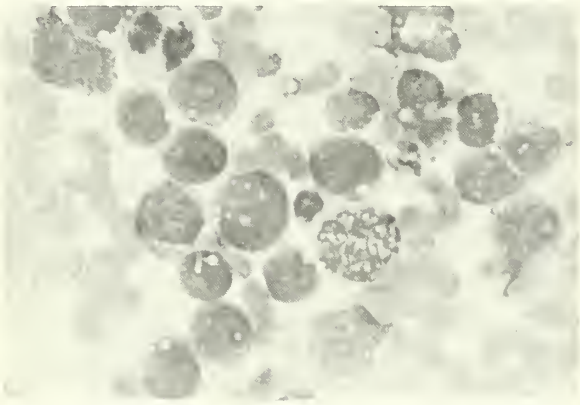

Figure 1.—Smear of the patient's second bone marrow aspirate showing complete replacement by vacuolated, "blast-like" cells. (440 ×)

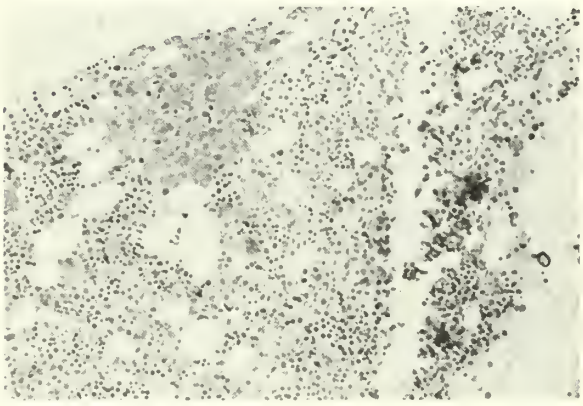

Figure 2.—Representative section of the patient's second bone marrow biopsy specimen showing invasion of normal bone marrow by metastatic oat cell carcinoma. Tumor necrosis was also present (not shown). (440 ×)

The patient continued to receive methotrexate, cyclophosphamide and vincristine as an outpatient. Bone marrow tolerance was not a problem during his second course of chemotherapy. He was readmitted to the hospital on January 7, 1977, with a rapidly enlarging and painful liver; the complete blood count was entirely normal. He died after a rapid downhill course. At autopsy, extensive involvement by oat cell carcinoma was found in liver, lung and kidney and in abdominal and thoracic nodes. Spinal marrow was found to be normal by gross and microscopic examination. The total course of illness from diagnosis was ten weeks.

Discussion

Metastases to bone from oat cell carcinoma of the lung are a common event without definite prognostic import other than that of disease outside the thorax.[4-6,10] Reported rates of involvement range from 19 percent to 46 percent.[4-6] Severe pancytopenia is not mentioned as a complication of marrow invasion in any of several series reporting successful treatment with combination chemotherapy.[4,6] Rapid onset of severe pancytopenia developed in our patient while he was receiving local radiotherapy for oat cell car-

cinoma. Although initial examination of marrow showed rare foci of tumor cells, a repeat examination showed complete replacement of bone marrow by tumor. The cells seen on smears were large, undifferentiated, vacuolated and "blast-like," showing no tendency to clump. The cells closely resembled those seen in acute lymphoblastic leukemia of childhood or the uncommon leukemic phase of Burkitt lymphoma.[11] Even with a previous cytologic diagnosis of oat cell carcinoma, there was confusion about the cause of the patient's pancytopenia. Serious consideration was given to a concomitant or alternate diagnosis of acute leukemia. A bone marrow biopsy specimen, available several days later, confirmed the diagnosis of carcinoma metastatic to marrow, again demonstrating the complementary nature of bone marrow aspiration and biopsy in this setting.[23]

Complete replacement of marrow by carcinoma has been noted by others, but seldom with smears that so closely mimic those seen in acute leukemia. The recent recognition of the high incidence of involvement of marrow by oat cell carcinoma[4-6] and the routine use of bone marrow aspiration and biopsy as a staging procedure in this disease[5,6] make it likely that such diagnostically confusing smears will be encountered more frequently in the future. Acute leukemia has also been recognized as a complication of chemotherapeutic treatment of other malignancies,[12,13] and it may arise as a complication of therapy for oat cell carcinoma as survival improves in this disease. This case should serve as a reminder that carcinoma, especially oat cell carcinoma, may be associated with pancytopenia and may present a picture similar to acute leukemia on routine smears of bone marrow aspirates.

Depression of bone marrow elements by multiple-drug chemotherapy has been stressed by some authors as the most common and most serious complication of such therapy for oat cell carcinoma.[6,10] However, in this patient, combination chemotherapy resulted in a complete remission of bone marrow disease with return of peripheral counts to normal. Previous reports of successful therapy of severe pancytopenia secondary to carcinoma of the breast or prostate have been restricted to patients who were responsive to hormonal therapy[7,9] or hormonal therapy plus chemotherapy.[14] Kiang and associates[14] have recently reported reversal of even severe marrow fibrosis with splenomegaly secondary to breast carcinoma with combination chemotherapy and hormonal therapy. This case and that reported by Kiang and co-workers illustrate that multiple-drug chemotherapy may be effective in reversing pancytopenia when it is due to extensive marrow

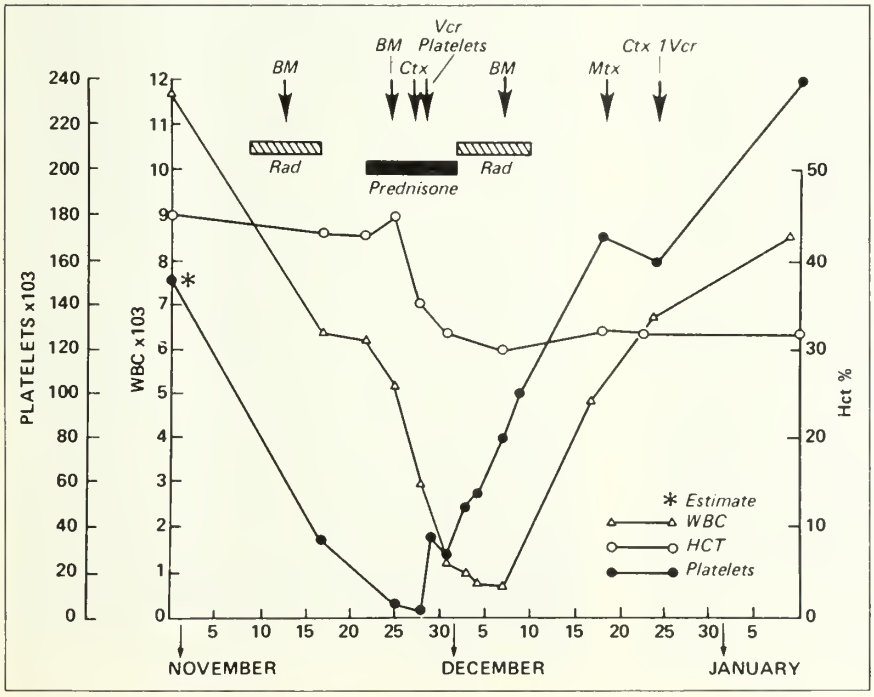

Figure 3.—Hematologic values in a patient with severe pancytopenia secondary to oat cell carcinoma metastatic to bone marrow. Note the rapid rise of both platelet and white blood cell counts after combination chemotherapy.

replacement by a responsive tumor, rather than depression of marrow function by previous chemotherapy. This concept of therapy is commonplace in the treatment of hematologic malignancies and may also become commonplace for carcinoma as response rate and therapeutic indices for these tumors improve.[15,16]

Summary

A 50-year-old man with oat cell carcinoma developed pancytopenia with severe thrombocytopenia while receiving localized radiation therapy. Smears of a bone marrow aspirate revealed complete replacement by "blast-like" cells resembling acute lymphoblastic leukemia. Bone marrow biopsy specimens resolved the diagnostic confusion, showing invasion of normal marrow by carcinoma. Prompt treatment with combination chemotherapy resulted in a complete bone marrow remission, documented with repeat biopsy and subsequently at postmortem examination. This case illustrates how metastatic carcinoma may occasionally mimic acute leukemia causing pancytopenia and replacement of marrow smears with abnormal cells. Pancytopenia in this instance should not be considered a contraindication to chemotherapy.

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Refer to: Eisenberg RL, Hedgcock MW, Wara WM, et al: Radiation-induced disease of the carotid artery. West J Med 129:500-503, Dec 1978

Radiation-Induced Disease of the Carotid Artery

RONALD L. EISENBERG, MD
MARCUS W. HEDGCOCK, MD
WILLIAM M. WARA, MD
R. BROOKE JEFFREY, MD
San Francisco

A RARE BUT SERIOUS complication of radiation therapy to the neck is the development of radiation-induced disease of the carotid artery. We wish to (1) present an additional case of radiation-induced carotid artery disease and (2) review the clinical and angiographic findings of this unusual entity.

Report of a Case

A 72-year-old man had a three-year history of dizzy spells, occasionally accompanied by blurred or double vision and lasting two to three minutes. These were brought on by rising suddenly or turning his head rapidly. Nine years previously he had undergone excision of a moderately well differentiated squamous cell carcinoma of the left pyriform fossa together with a left radical neck resection. Postoperatively he received irradiation therapy utilizing a cobalt 60 apparatus to a single left neck portal (14×8 cm). The maximum left neck skin dose was 7,154 R with a calculated tumor dose at 4 cm of 6,045 R given in 42 fractions over 60 elapsed days. At completion of irradiation the residual tumor had disappeared, and the patient has been free of recurrent disease for the past nine years.

On admission the left carotid pulse was absent. A left subclavian bruit was present, and a blood pressure difference was noted between the two arms (right 130/70 mm of mercury; left 108 by palpation). Findings on physical examination were otherwise within normal limits. Angiographic studies showed that a 7-cm, smooth, 95

From the Department of Radiology, University of California, San Francisco, School of Medicine, and the Veterans Administration Hospital (Drs. Eisenberg, Hedgcock and Jeffrey), San Francisco, and the Division of Radiation Oncology (Dr. Wara), University of California, San Francisco.
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Reprint requests to: Ronald L. Eisenberg, MD, Radiology Service, Veterans Administration Hospital, 4150 Clement Street, San Francisco, CA 94121.

percent stenosis involved the left common carotid artery from 5 cm above its origin from the aortic arch to 2 cm below the carotid bifurcation (Figure 1). The bifurcation showed no evidence of atherosclerotic disease. There was a 1-cm segment of severe narrowing of the left subclavian artery, 5 cm distal to the origin of this vessel from the aortic arch (Figure 2). There was a short, severely narrowed segment of the right internal carotid artery 2 cm above the bifurcation and a relatively long area of moderate narrowing in the common carotid artery (Figure 3). Minimal irregularity of the proximal portion of the right subclavian artery (Figure 3) was also noted.

Figure 1.—Radiograph showing a long smooth stenosis **(arrow)** of the left common carotid artery.

At surgical operation, findings consistent with atherosclerotic disease were seen involving both the right common carotid and internal carotid arteries; transendarterectomies were done in these areas. Since the patient's symptoms had decreased, and in view of the difficulty of operating on previously irradiated tissue,[1] decision was made not to operate on the left carotid artery.

Discussion

Ours is the sixth reported case of a patient with angiographic demonstration of radiation-induced disease of the extracranial carotid artery. Two general patterns of involvement have emerged. One is severe smooth narrowing of the carotid artery over a long segment that spares the carotid bifurcation (where atherosclerotic disease generally occurs) while involving areas not usually affected by atherosclerotic disease. In our patient, a 7-cm segment of the common carotid artery was severely narrowed; in the case reported by Levin-

Figure 2.—Radiograph showing short, severely narrowed segment of the left subclavian artery **(white arrow).** The severe stenosis of the proximal left common carotid artery is also shown **(black arrow).**

son and co-workers,[2] a long segment of the internal carotid artery was similarly affected. In neither instance did the carotid bifurcation show atherosclerotic change. In Conomy and Kellermeyer's patient,[3] thrombotic occlusion of the internal carotid was seen; in addition, a serpentine intraluminal defect was seen at the carotid bifurcation. The other manifestation of radiation-induced disease of the carotid artery is diffuse, irregular ulcerative lesions. The lesions may be associated with short stenoses[2] or with moderate dilatation[4] of the carotid artery. As with the long smooth stenoses, the ulcerative lesions tend to occur at sites usually unaffected by atherosclerotic disease.

The changes in the right carotid artery seen at surgical operation in our patient were thought not to be directly attributable to irradiation disease. However, since these areas were in the region of the radiation port (though well removed from the level of maximum dosage) the possibility that irradiation accelerated atherosclerotic change must be considered.[2-19]

Figure 3.—Radiograph showing short, severely narrowed segment of the right internal carotid artery 2 cm above bifurcation **(white arrow)** and a large area of moderate narrowing of the right common carotid artery **(black arrow)**. Minimal irregularity of the proximal portion of the right subclavian artery is also seen.

Radiation-induced disease has also been described in the subclavian artery after radiation therapy for carcinoma of the breast.[5,6,15] Angiography in these cases revealed short segmental stenoses, similar to the appearance in our case. Radiation-induced disease involving aorta,[14,20] iliac arteries,[5,11] femoral arteries[5,9,16,17] and coronary arteries,[21] has also been described.

Radiation-induced damage to the carotid artery secondary to radiation therapy to the neck can cause the clinical manifestations of cerebrovascular insufficiency. Of the six cases with adequate clinical data previously reported, three had sudden hemiparesis.[2,5,7] In one of these,[7] there had been a single previous episode of hemispheric ischemia which cleared in three days; in the other patients,[2,3] no history of previous transient ischemic attack could be elicited. Two patients[2,4] had transient ischemic attacks only. In one patient,[4] the ischemic attacks were hemispheric, consisting of unilateral hand and leg weakness but no visual symptoms. In the other,[2] there were daily attacks of blindness for six months with no motor symptoms. One patient had a single sudden "drop attack" attributed to generalized cerebrovascular insufficiency due to combined carotid and vertebral lesions.[2] In our patient, the overriding symptom was generalized cerebral insufficiency with decreased perfusion due to stenoses of both common carotid arteries, the right internal carotid artery and the left subclavian artery proximal to the origin of the left vertebral artery. The visual symptoms were attributable to the carotid lesions alone.

Several mechanisms account for the variable symptomatology in patients with radiation-induced disease of the carotid arteries.[2] Reduced retinal perfusion produces transient visual disturbances; reduced cortical perfusion produces transient hemispheric ischemic attacks. Emboli from ulcerated lesions in the carotid artery can evoke sudden hemiparesis as well as hemispheric ischemic attacks and transient visual disturbances. When decreased blood flow in the carotid system is combined with decreased perfusion in the vertebrobasilar system (for example, vertebral or subclavian artery stenoses), generalized cerebral ischemia leading to "drop attacks" and dizziness can occur.

Pathological examination of specimens from patients with radiation-induced disease of large elastic arteries has shown findings consistent with

premature atherosclerosis and perivascular fibrosis.* There is marked thickening of the arterial wall which may lead to partial or total obstruction of arterial blood flow. This thickening involves all portions of the arterial wall, but primarily the adventitia. A narrow band of fibrin covering the intima has been described, and necrosis of the intima with intense subintimal edema has been noted. Thinning and fragmentation of elastic fibers is common. Polymorphonuclear neutrophilic infiltration is widespread in areas of intimal and subintimal necrosis. Fat-laden macrophages and radiation fibroblasts are often seen.

Similar pathologic findings of accelerated atherosclerosis have been experimentally demonstrated to occur following irradiation of large elastic arteries in animals. Smith and Lowenthal[22] showed that irradiation in mice produced an increase of ground substance and fraying of the elastic membrane comparable with physiological aging. Gold[8] produced intimal proliferation with medial degeneration and fibrosis by radiating hypercholesterolemic rats; Lamberts and DeBoer[12] produced similar effects in hypercholesterolemic rabbits. Sams[19] described similar changes in the vessel walls in irradiated mice and stressed the severe degree of periarterial fibrosis, which he believed constricted the artery. Lindsay and associates[13] created similar atherosclerotic changes by irradiating segments of the aorta in normal dogs. Marcial-Rojas and Castro[14] studied radiation injury to elastic arteries in patients treated for neoplastic disease and described rupture of major blood vessels with fatal hemorrhage.

The exact pathogenesis of radiation-induced disease is unclear. Rubin and Casarett[18] described occlusive changes in the vasa vasorum of large arteries after irradiation. These occlusive changes could lead to ischemia of the arterial wall with subsequent generalized necrosis. Marcial-Rojas and Castro[14] suggested that the initial damage is caused by a local tissue effect, enhanced by the subsequent obliterative vascular changes in the nutrient arteries.

In view of the large numbers of patients whose necks are radiated to high levels for upper airway neoplasm and mediastinal adenopathy, the occurrence of radiation-induced disease of the carotid arteries appears to be rare. However, it must be considered in any patient with transient hemispheric or visual ischemic attacks, sudden hemiparesis, or generalized cerebrovascular insufficiency who has previously undergone radiation therapy to the neck. Angiography may demonstrate the characteristic findings of either a long smooth narrowed segment or a diffuse ulcerated segment, both in areas that usually are not affected by atherosclerotic disease.

*References 2-7, 9, 10, 14-18, 20, 21.

Summary

Radiation-induced disease of the carotid artery is a rare but serious complication of radiation therapy to the neck. Clinical manifestations include transient hemispheric and visual ischemia, sudden hemiparesis and generalized cerebrovascular insufficiency. Angiographic studies may show severe smooth narrowing of the carotid artery over a long segment or diffuse irregular ulcerative lesions. These tend to occur at sites usually unaffected by atherosclerotic disease.

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Refer to: Abrams JJ, Sandler JA: Recurrent Graves disease spanning 24 years. West J Med 129:504-506, Dec 1978

Recurrent Graves Disease Spanning 24 Years

JEFFREY J. ABRAMS, MD
JEFFREY A. SANDLER, MD
San Diego

THE THERAPY of the diffuse toxic goiter of Graves disease is directed at the thyroid gland, the effector of the disease, rather than the underlying stimulus to its overactivity. Thyroidectomy and radioactive iodine are employed in an attempt to eliminate enough tissue to render the patient euthyroid. Once the euthyroid state is achieved, permanent control of the disease occurs in 92 percent to 98 percent of the patients treated by thyroidectomy[1] and in greater than 99 percent treated with radioactive iodine.[2] The purpose of this communication is to report the unusual recurrence of Graves disease 17 years following attainment of euthyroidism.

Report of a Case

A 19-year-old white man presented to Tripler Army Hospital in 1953 with complaint of four months of nervousness, weight loss and weakness. He had no prior history of thyroid disease and no family history of endocrine abnormalities. On physical examination he was noted to be thin and hyperkinetic; the thyroid gland was found to be diffusely enlarged and smooth. Pulse rate was 120 beats per minute; there was bilateral proptosis. Basal metabolic rate (BMR) was +55 percent, the protein-bound iodine (PBI) value was 22 μg per dl (normal 4 to 8) and the serum cholesterol level was 139 mg per dl. A diagnosis of Graves disease was made and therapy with propylthiouracil and Lugol solution was initiated for two months followed by a subtotal thyroidectomy. Seventy grams of thyroid tissue were resected and the histology showed a diffusely hyperplastic gland with lymphocytic infiltration, compatible with Graves disease. The patient was discharged and returned to duty receiving no medications and with prompt dissolution of the hyperthyroid symptoms. BMR at that time was −6 percent.

ABBREVIATIONS USED IN TEXT
BMR = basal metabolic rate
PBI = protein-bound iodine
RAIU = radioactive iodine uptake
RIA = radioimmunoassay

The patient was well until 1959 when he complained of the recurrence of symptoms including weight loss, nervousness, irritability, tremor, heat intolerance and enlargement of the thyroid gland. He presented to the Veterans Administration (VA) Clinic in Los Angeles where he was found to have a pulse rate of 100, a tremor, proptosis, a PBI of 10.2 μg per dl and a cholesterol level of 129 mg per dl. BMR was +34 percent and radioactive iodine uptake (RAIU) at 6 and 24 hours was 44 percent. An enlarged unilobular thyroid gland was noted on the scan. A diagnosis of recurrent Graves disease was made and in May 1959 treatment was begun with 3.3 mCi of iodine 131. Following this treatment clinical improvement was seen. One year later the patient was clinically and chemically euthyroid.

The patient was then transferred to the VA Outpatient Clinic, San Diego, where he presented in 1965 with a weight gain of 12 pounds, cold intolerance, easy fatigability and hoarseness and had a resting pulse of 80 beats per minute. On physical examination, his thyroid gland was not palpated. Laboratory studies gave the following values: PBI, 3.6 μg per dl; RAIU, 11 percent at 6 hours and 17 percent at 24 hours; photomotogram, 380 msec (normal, 255 to 380 msec[3]) and serum cholesterol, 200 mg per dl. Results of physical examination and laboratory data were most consistent with hypothyroidism, but it was elected to follow the case without treatment. The symptoms remitted and no treatment was required.

His admission to the San Diego VA Hospital in January 1977 was prompted by a one-year history of increasing fatigue, restlessness and two syncopal episodes. On examination he had a pulse rate of 100 beats per minute, a tremor, stare, mild proptosis, and diffuse enlargement of the left lobe of the thyroid gland estimated to weigh 50 grams. The thyroxine (T_4) value by radio-

From the Division of Metabolic Diseases, Department of Medicine, University of California San Diego Medical Center, San Diego.

Submitted, revised, February 13, 1978.

The WESTERN JOURNAL's style regarding eponyms is that they are not written in the possessive form; therefore, Graves disease, Ewing sarcoma and Paget disease. An explanation may be found on page 78 of the July 1978 issue.

Reprint requests to: Jeffrey A. Sandler, MD, 4094 Fourth Ave., San Diego, CA 92103.

immunoassay (RIA) was 18 (normal, 4.5 to 12), free thyroxine index was 18 (normal, 3.4 to 12.7), and triiodothyronine (T_3) by RIA was 305 ng per dl (normal, 80 to 170). A long-acting thyroid stimulator (LATS) titer was positive, as were antithyroid antibodies. Serum cholesterol was 147 mg per dl, and the RAIU was 29 percent at 4 hours and 35 percent at 24 hours. The scan again showed an enlarged unilobular thyroid gland. The patient was treated with 10 mCi of radioactive iodine and was euthyroid clinically and chemically three months later with a T_4 by RIA of 8.8 and T_3 by RIA of 180 ng per dl.

Discussion

Failure of spontaneous remission is the rule rather than the exception in patients with Graves thyrotoxicosis. The remission rate in patients treated with antithyroid drugs has been steadily decreasing, paralleling an increase in dietary iodine, and now approximates 20 percent.[4] The low likelihood of a drug remission has placed an emphasis on therapy with radioiodine and thyroidectomy. Hypothyroidism is now considered an easily treatable, acceptable and even desirable complication of iodine 131 therapy.[5] Thyroidectomy may produce a lesser incidence of hypothyroidism but the rate of recurrent hyperthyroidism is greater[6] and may occur many years later.[7]

Although it is well-known that radioiodine usually produces permanent elimination of Graves disease, this has not been emphasized in the most recent literature. Blomfield and his co-workers in reviewing 192 cases of iodine 131 therapy for Graves disease reported that no patients relapsed at a longer interval than one year after therapy.[8] Volpe and associates, reporting on their experience at Toronto General Hospital with iodine 131 therapy between 1950 and 1958, found no late recurrences in a series of over 400 patients.[9] Goldsmith in his review from the Mayo Clinic states that in general iodine 131 treatment is permanent.[10] Our review of a large series reporting treatment of Graves disease by iodine 131 gives a recurrence rate of 0.3 percent (Table 1); recurrence is an exceptional event after effective clinical control has been achieved for one year with radioiodine. However, in this patient hyperthyroidism recurred despite radioiodine administration and may possibly be related to the lower dose used. This is an example of how the recent emphasis on the use of lower doses of radioiodine to avoid hypothyroidism exposes the patient to a different risk, recurrent hyperthyroidism, even many years after apparently successful correction of the thyrotoxicosis.

TABLE 1.—*Incidence of Recurrent* Graves Disease Following ^{131}I Treatment*

Source of Data	*Number of Patients Treated*	*Recurrence of Graves Disease (No. of Cases)*
Chapman & Maloof, 1955[11]	477	0
Clark & Rule, 1955[12]	262	2
McCullagh, 1956[13]	1,235	2
Werner et al, 1957[14]	282	3
Cassidy & Astwood, 1959[15]	200	0
Blomfield et al, 1959[8]	192	0
Eller et al, 1960[16]	1,040	7
Beling & Einhorn[2]	218	1
Volpe et al, 1961[9]	403	0
Goldsmith, 1972[10]	248	0
TOTAL	4,557	15

*Following at least one year of euthyroidism

We report the case of a patient with Graves disease rendered euthyroid by surgical operation with a recurrence six years later. This was followed by an apparently successful treatment with iodine 131 and resolution of hyperthyroid symptoms lasting 17 years, eventuating in a third episode of hyperthyroidism. The possibility that there was actually persistent rather than recurrent hyperthyroidism cannot totally be excluded because in 1965 a determination of T_3 by radioimmunoassay was unavailable. However, the patient's clinical symptoms and signs were more suggestive of hypothyroidism than of any other metabolic state.

We wish to emphasize that therapy with radioiodine is essentially a cure for the thyrotoxicosis of Graves disease, and to report a rare exception occurring in a patient treated with a low dose of radioiodine.

Summary

The case of a 43-year-old man with recurrent hyperthyroidism is described. The patient initially presented with Graves disease 24 years earlier and was treated with a subtotal thyroidectomy. Six years later thyrotoxicosis recurred and he was treated with iodine 131. After radioiodine therapy, the patient was euthyroid for 17 years until return of hyperthyroid symptoms prompted repeat radioiodine treatment. Review of 4,557 cases of Graves disease treated with iodine 131 shows a recurrence rate of thyrotoxicosis of 0.3 percent after one year of euthyroidism, support-

ing the concept that radioiodine is virtually curative. The present case serves to illustrate an exception.

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Establishment of an IV Route in Obstetric Patients

FUNDAMENTAL TO THE ADMINISTRATION of any anesthetic is the presence of a secure intravenous route. The placement, however, of something as large as a 16-gauge Intracath® can be traumatic to the patient, so that I strongly urge . . . putting a local anesthetic bleb into your point of puncture. Most people tend to place the intravenous needle bevel side up into the vein which increases the risks of perforating the vein and having a failed intravenous. Hence, I would recommend that a bevel-down introduction of the Intracath be done. Once the Intracath is in place, several options are now available if sudden large amounts of fluids need to be infused, such as, for example, blood. You can then go to a much easier form of intravenous administration, which is not as secure and consequently probably should be limited to use in unconscious patients, and that is the placement of a 16-gauge Butterfly®. Because it is so short, the Butterfly will tend to flow more readily than a large, long 16-gauge, either extracath or Intracath.

—WILLIAM GOTTSCHALK, MD, *Chicago*

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Concerning Vitamins

To the Editor: In the March 1978 issue of the Western Journal Dr. Richard R. Babb, in his article "Cirrhosis Due to Hypervitaminosis A," states that "vitamins are not synthesized in the body. . . ."

I have been under the impression that vitamin D is manufactured in the skin when the skin is exposed to sunlight, that vitamin K is manufactured by bacteria in the intestinal tract and that vitamin A can be manufactured in the human body from the pigments that are present in certain vegetables such as corn and carrots.

Could you have this situation clarified for me and other readers of the journal?

JOHN ERHARDT, MD
Laguna Hills, California

* * *

Dr. Erhardt's letter was referred to Harold A. Harper, PhD, who replies as follows:

To the Editor: I found the article by Dr. Richard R. Babb very interesting, although not surprising. Of all the vitamins only A and D can definitely be toxic if consumed for a prolonged period in dosages not much above the recommended daily allowances. Of course toxic doses can only be obtained from pharmaceutical preparations; rarely, if ever, from natural foods.

To answer specifically the questions raised in connection with the statement that vitamins are not synthesized in the body, this is in general a true statement, except that it is not universal in a strict sense and does not obtain with all species of animals. For example, except for primates (and guinea pigs) all animals can synthesize vitamin C. If we confine the situation to the human species the following facts would obtain with respect to the fat soluble vitamins.

Virtually all of the vitamin A obtained from the diet occurs as the plant pigment β-carotene which is widely distributed in leafy green and yellow vegetables. In the normal human this carotene is converted to vitamin A. The vitamin A itself is almost entirely confined to fish liver oil and the viscera of marine fish. Carotene, even when consumed in large amounts from foods, is not toxic although it may accumulate in the tissues if taken in excess. When the excess ingestion of carotene stops this compound is promptly cleared from the body.

The precursors of vitamin D are sterols closely related to cholesterol. The major precursor of vitamin D is a sterol, namely 7-dehydrocholesterol, which is synthesized in the human body. When this sterol is exposed to shortwave ultraviolet light, as by sunlight, on the skin where the precursor sterol is found, the vitamin D is manufactured, although in recent work it has been found that the irradiated 7-dehydrocholesterol must be further chemically modified in the liver and later in the kidney to form 1, 25, dihydroxy-7-dehydrocholesterol, which is actually the active form of vitamin D as it acts on the tissues of the body. Cholecalciferol is the term now applied to the irradiated product from the precursor synthesized in the body, 7-dehydrocholesterol. Thus active vitamin D produced by a series of synthetic processes in the body is 1, 25-dihydroxycholecalciferol. It has also recently been shown that the action of vitamin D is more like that of a steroid hormone than that of a vitamin. In any event the intake of excess cholecalciferol (vitamin D_3) or ergosterol irradiated to form vitamin D_2, as might be found in pharmaceutical preparations, is also very toxic if taken over long periods.

Reference was also made to vitamin K, another fat soluble vitamin. This compound also occurs fairly widely in natural foods and is indeed produced by the activity of putrefactive bacteria within the intestinal tract. As a result dietary deficiency of vitamin K probably never occurs. The important matter is that all the fat soluble vitamins (vitamins A, D, E and K) require that digestion and particularly absorption of fats be normal if these vitamins are to be absorbed. In

the case of vitamin K the most common cause of deficiency of this factor is the existence of a syndrome associated with impaired lipid ingestion and absorption. Examples are obstructive biliary disease or widespread malabsorption, such as in sprue or celiac disease. Another clinical event relating to vitamin K deficiency is the result that occurs after prolonged oral therapy with drugs (such as sulfaguanidine or succinylsulfathiazole) capable of suppressing vitamin K-producing bacteria.

I think it must be observed that the difference of opinion manifested in the article and Dr. Erhardt's letter are, as is not infrequently the case, mainly due to faulty communication and failure to be specific about the ability of vitamins to be obtained in some instances from other than dietary sources.

HAROLD A. HARPER, PhD
Professor of Biochemistry
Dean, Graduate Division
University of California, San Francisco

Management of Tetanus

To the Editor: We share Dr. Herbert Webb's concern for the respiratory care of patients with tetanus (Henderson DK, Tillman DB, Webb HH, et al: Infectious disease emergencies: The clostridial syndromes—Teaching Conference, University of California, Los Angeles and Harbor General Hospital, Torrance [Specialty Conference]. West J Med 129:101-120, Aug 1978). However, we disagree with the suggested management in several areas.

Dr. Webb advocates the use of diazepam as the preferred agent to facilitate intubation should sudden airway obstruction due to laryngeal spasm occur. We suggest that succinylcholine, administered intravenously in a dose of 1 mg per kg of body weight, will relieve laryngeal spasm and provide optimal relaxation for intubation in this situation. Since the condition of virtually all patients with tetanus will deteriorate after initial diagnosis and their admission to the hospital, we would elect the following course of airway management: nasotracheal intubation after the first muscle spasm, and then assessment over the next several days to determine ultimate severity of the disease and the possible need for long-term airway management with tracheostomy. Modern endotracheal tubes using a high volume, low pressure cuff may be left in place for two weeks or longer; the incidence of complications associated with their use is no greater than that seen with the use of a tracheostomy tube and there is much less of an operative hazard. For those who elect a more conservative early course of airway management, a laryngoscope, an endotracheal tube and succinylcholine should be kept at the bedside; personnel familiar with their use must be immediately available should laryngeal spasm occur.

We would also question Dr. Webb's use of the sigh in mechanically ventilated patients in whom 12 to 15 ml per kg of body weight tidal volumes are used. Such maneuvers cause very high inflation pressures to be generated with a consequent higher risk of pulmonary barotrauma; maintenance of optimal functional residual capacity (FRC) can be more easily obtained, and with less risk, by maintaining minimal levels of end-expiratory pressure. Sighs have not been found helpful in maintaining optimal FRC in paralyzed patients ventilated with tidal volumes of 12 to 15 ml per kg.

For patients with severe tetanus where paralysis becomes necessary to control muscle spasms, d-tubocurarine has long been the mainstay of nondepolarizing blocking agents used. It may cause hypotension, however, by histamine release and ganglionic blocking. It has recently been shown that metocurine (Metubine®) lacks this hypotensive effect while producing muscle paralysis.[1] This agent, then, might be a better choice than d-tubocurarine in producing long-term paralysis in these patients.

DAVID D. ALFERY, MD
L. ANDREW RAUSCHER, MBBS, FFARCS
Department of Anesthesiology
University of California, Medical Center
San Diego

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* * *

Dr. Webb Replies

To the Editor: I think it is important to respond to several of the comments made by Drs. Alfery and Rauscher. Actually, I did not advocate the use of diazepam as the preferred agent to facilitate intubation and the setting of laryngeal spasm in tetanus. I did say that it was crucial to use "a paralytic agent or muscle relaxant (preferably diazepam)." I have found diazepam to be quite adequate on several occasions in the setting of laryngeal spasm in tetanus. It is true that succinyl-

choline is accepted as the agent of choice for a paralytic agent needed for immediate onset of action. However, I have been hesitant to advocate its use in tetanus because of its widely known complication of hyperkalemia in the presence of muscle trauma and numerous neuromuscular diseases.[1,2] It has been stated that significant hyperkalemia can occur after succinylcholine in tetanus,[3] but I cannot find good documentation of this. Succinylcholine was used to manage one patient with tetanus requiring paralytic therapy but serum potassium values were not assessed.[4] My recommendation is to give diazepam intravenously in a large dose and if this is not successful in facilitating intubation, to proceed rapidly to the use of succinylcholine as recommended by Alfery and Rauscher, and to be aware of the possibility of acute and clinically significant hyperkalemia.

Experience in tetanus has shown that not all patients require an aggressive early course of airway management with nasotracheal intubation but certainly I agree with the caveat that if conservative early airway management is elected, the patient must be carefully observed, an intravenous infusion line should be ready and succinylcholine, diazepam, and personnel and equipment for immediate airway control should be available.

Tidal volumes of 10 to 15 ml per kg of body weight do not cause "very high inflation pressures" in patients with normal lung compliance and are rather routine in many respiratory care centers for both paralyzed patients and others and have been found to maintain adequate functional residual capacity without the use of sighs in numerous patients. However, in totally paralyzed patients many of us still use deep sighs to rejuvenate surfactant and help to prevent diffuse microatelectasis which otherwise occurs. I have not routinely used positive end-expiratory pressure in paralyzed patients because of the high incidence of thromboembolic complications in these patients even without the use of positive end-expiratory pressure which may itself predispose to that problem. This seems to be particularly relevant to patients with tetanus as indicated in my discussion.

Although d-tubocurarine has been widely used as a paralytic agent in many forms of respiratory failure and in tetanus, pancuronium is probably a better agent because of its ease of use and essential freedom from complications including hypotension which d-tubocurarine may cause as indicated by Drs. Alfery and Rauscher. In essence, I agree with them that it should not be used in tetanus for the reason they state, especially since autonomic insufficiency and hypotension are not infrequent problems in patients with tetanus. I see little reason to use metocurine in place of pancuronium which has now had extensive clinical experience.[5]

HERBERT H. WEBB, MD
San Pedro Peninsula Hospital
San Pedro, California

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Prevalence of Amebiasis

To the Editor: In the September issue of the journal (West J Med 129:241-242, 1978) Dr. Edward Markell made a spirited attack on my position that endemic amebiasis must be quite uncommon, although it is a problem with travelers and in the homosexual community.

I called Dr. Markell, who proved to be a gracious and learned gentleman, and we were able to resolve most of our differences. Both agree that we found amebae in one to two percent of submitted specimens during the past year (actually 1.1 percent for Valley Memorial Hospital, Livermore, California and 1.7 percent for Kaiser-Permanente Medical Center, Oakland, California). Interestingly, we each found exactly 4 percent of specimens positive for Giardia. My interpretation of this is that Dr. Markell's astute clinicians and competent technologists are detecting most of the amebiasis in the Kaiser-Permanente medical population, giving about 100 to 150 cases per year in a population of about 750,000, a rate similar to my previous speculation.

Dr. Markell, on the other hand, thinks that sampling a healthy population would yield nearly the same percentage of positives. He has some basis for his opinion, as he did some unpublished work on Navy personnel that showed a significant asymptomatic prevalence, and also found a num-

ber of carriers among food-handler job applicants.

I would reject these studies on the grounds that they were done years ago, that Navy people travel and that the food-handler sample was probably weighted with Mexican immigrants. Since the Permanente hospitals have put food preparation out to contract, there are no longer any food handlers to examine. At our institution, we have never found amebae in a preemployment examination. The number of people examined each year, however, is only about 150, and is not statistically significant. In all the amebiasis cases I looked into there was an exposure or an enteric disease thought by a clinician to be possibly due to parasites. I, therefore, believe that an examination of healthy persons will not show a large number of asymptomatic carriers.

Obviously, the only way to resolve this problem is to examine a large number of stool specimens from healthy people. Dr. Markell and I have agreed to do this on a cooperative basis. Pending the result of such a study, I maintain my opinion that Dr. Krogstad of the Center for Disease Control was correct in stating "endemic amebiasis is rare. . . ."[1]

CLAUDE O. BURDICK, MD
Pathologist
Director of Laboratories
Valley Memorial Hospital
Livermore, California

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EDTOR'S NOTE: We hope to learn the result of this cooperative study.

—MSMW

Cumulative Injury

TO THE EDITOR: I read with considerable interest "Cumulative Injury" by Dr. Joseph LaDou in the September 1978 issue of the *Western Journal.*

For several years I have evaluated, primarily for insurance companies and their attorneys, people who claim that "stress and strain" of their employment have caused heart disease, hypertension, indigestion, nervousness, etc. I have marveled at the enormous costs of the multiple consultations and legal procedures seemingly necessary for the evaluation of each and every symptom the patient complains of, however insignificant.

I am in agreement with Dr. LaDou's conclusions; the situation is entirely out of hand. In my opinion the vast majority of claims are unwarranted; as the ailments are really the usual degenerative conditions we all get as we age or the claimants are people who are unhappy with their job, for various reasons.

I have noticed that plaintiff's attorneys generally ask their clients what disease or symptoms they have and then frequently suggest that their jobs *may* have aggravated their conditions. The lawyers then send the client to a doctor of the *lawyers'* choice, invariably one or two or three doctors, always the same ones, no matter what the symptoms are. These doctors always seem to conclude that the job was "stressful" and aggravated the patient's symptoms or medical complaints.

In my opinion, these doctors should be considered "guns for hire"; the lawyers know in advance the conclusions to be reached by these so-called impartial consultants.

The solution would be the establishment of a panel of medical *experts* paid for their time, but not representing either the plaintiff or defendant. These experts would review all claims and summarily reject those that have no merit. This can easily be done in the vast majority of cases by reviewing the medical records only. The unresolvable cases should then proceed through the usual judicial channels.

A. S. WEISSBEIN, MD
San Bernardino, California

Refer to: Coskey RL: Cardiopulmonary resuscitation: Impact on hospital mortality—A ten-year study (Health Care Delivery). West J Med 129:511-517, Dec 1978

Cardiopulmonary Resuscitation

IMPACT ON HOSPITAL MORTALITY—A TEN-YEAR STUDY

RICHARD L. COSKEY, MD, *Burbank, California*

The effectiveness of cardiopulmonary resuscitation as a vital aspect of health care delivery in hospital was the basis for a ten-year study. All instances of cardiac arrest occurring outside the operating room and nursery were included.

Variations in degrees of success of cardiopulmonary resuscitation as related to the duration of the program, differences among varying subsets such as patients' type of illness and hospital location (emergency room, coronary care unit, intensive care unit or nursing floor) at the time of cardiopulmonary arrest, are presented. The relationship between cardiopulmonary resuscitation frequency and success with increasing instrumentation is reviewed. A simple technique for expressing effect of cardiopulmonary resuscitation on hospital mortality is presented.

The study shows the ability of a community hospital to establish, maintain and document a high level cardiopulmonary resuscitation program.

CARDIOPULMONARY RESUSCITATION (CPR) programs in hospitals have developed into a vital aspect of health care delivery. The effectiveness of CRP programs and relationship to patient age has been well outlined.[1-9]

Government regulations[10] as well as the Revised Joint Statement by the California Medical Association, California Nurses' Association and California Hospital Association[11] and Accreditation Manual for Hospitals[12] have focused on in-hospital CPR programs.

Information on the effect of CPR on modifying in-hospital mortality has not been well outlined. The relationship of patients' primary illness and patient location to the presence or absence of electrocardiographic monitoring on CPR performance has not been presented in detail.

A review of ten years of CPR experience and its modification of hospital mortality forms the basis for this report.

From St. Joseph Hospital Medical Center, Burbank, California.
Submitted, revised, June 12, 1978.

Reprint requests to: Richard L. Coskey, MD, Cardiology Consultants Medical Group, Inc., 18370 Burbank Blvd., Suite 707, Tarzana, CA 91356.

ABBREVIATIONS USED IN TEXT
CCU = coronary care unit
CPR = cardiopulmonary resuscitation
ER = emergency room
ICU = intensive care unit

Methods and Patient Population

St. Joseph Medical Center is a community hospital with 411 beds, excluding bassinets. Occupancy had gradually risen from 116,000 in 1967 to 126,000 in 1974. Occupancy data for the first two years of the study were collected using slightly different techniques and are, therefore, not included. There was an approximate 9 percent increase in occupancy over the last eight years of the study. The total number of patients discharged remains in the range of 20,000 per year for the last six years of the study. Patients with a primary cardiac diagnosis constituted 7 percent to 10 percent of the hospital population. The number of electrocardiographic monitors (excluding the surgical suites) increased from 6 in 1964 to 77 in 1974. The CPR program was organized within the Department of Nursing under the guidance and direction of physicians. Full-time physicians trained in emergency medicine have been employed 24 hours a day in the emergency rooms since July 1, 1973. Details of the program have been previously reported.[1]

Cardiopulmonary arrest is defined as the sudden and unexpected cessation of respiration or effective circulation. A patient whose death is anticipated at the end of a chronic illness would not be described as having a cardiopulmonary arrest. All patients were resuscitated if they suffered a cardiopulmonary arrest which could have occurred within the four minutes preceding discovery when there were no physician's orders to the contrary.

Resuscitation was usually initiated by nursing personnel within one minute of onset of asystole or ventricular fibrillation. The interval between arrest and the onset of resuscitation could not be estimated in many of the nonmonitored patients.

Patient data are divided into four categories:

(1) Long-term survivors (patients who have undergone successful resuscitation and have been discharged from the hospital with cerebration unchanged from pre-CPR status);

(2) Short-term survivors (patients successfully resuscitated with cerebration unchanged from pre-CPR status but who died of underlying disease before hospital discharge);

(3) Persons in whom there was successful resuscitation but brain damage, and

(4) Failure (a patient who could not be successfully resuscitated).

TABLE 1.—*Overall Results of Cardiopulmonary Resuscitation Experience, 1965-1974*

	Long-Term Survivors (Percent in Parenthesis)	*Short-Term Survivors (Percent in Parenthesis)*	*Brain Damage (Percent in Parenthesis)*	*Failure (Percent in Parenthesis)*	*Total*
1965	8 (16)	5 (10)	0 (0)	37 (74)	50
1966	14 (25)	4 (7)	9 (16)	30 (53)	57
1967	23 (22)	10 (10)	1 (1)	69 (67)	103
1968	26 (22)	15 (14)	2 (2)	76 (64)	119
1969	30 (23)	22 (17)	0 (0)	79 (60)	131
1970	27 (21)	17 (13)	5 (4)	77 (61)	126
1971	22 (16)	31 (23)	5 (4)	76 (57)	134
1972	35 (27)	37 (29)	4 (3)	52 (41)	128
1973	44 (28)	30 (19)	6 (4)	78 (49)	158
1974	48 (32)	27 (18)	10 (7)	64 (43)	149
Total	277 (24)	198 (17)	42 (4)	638 (55)	1,155

The critical care units comprise emergency room (ER), coronary care unit (CCU) and intensive care unit (ICU). The CCU had electrocardiographic monitoring capabilities for all beds and the ER and ICU for selected beds, in the early years of this study. Later, the ICU also had electrocardiographic monitoring capabilities for all beds.

The remainder of the hospital units were identified as noncritical care nursing units. They initially had no fixed electrocardiographic monitoring capabilities. In the latter years of the study, one nursing unit (32 beds) had complete and another had extensive electrocardiographic telemetry monitoring.

Previous in-hospital studies had included a large number of CPR's occurring in the operating theater.[6] This study excludes arrests in the operating theater.

Overall Results

Table 1 summarizes overall results of the ten-year study. Figure 1 combines short-term and long-term survivors and shows a gradual increment in both number of patients and the percentage of patients successfully resuscitated. Of patients who received CPR in the last three years of the study, 50 percent were short-term or long-term survivors. Figure 2 relates hospital occupancy to the number of electrocardiographic monitors.

Illness

Most of the patients in whom CPR was used, as well as those successfully resuscitated, had underlying cardiac disease. Most of those with cardiac disease were being treated for acute myocardial infarction.

Two thirds of the patients undergoing CPR as well as two thirds of the long-term plus short-term survivors had cardiac disease as the underlying cause of their cardiopulmonary arrest. More than two thirds of the group with cardiac disease had acute myocardial infarction as the primary cause of cardiopulmonary arrest. Of the total, 7 percent had pulmonary parenchymal disease, 5 percent had pulmonary embolization, 7 percent had central nervous system pathologic conditions, 3 percent had cancer and less than 2 percent had drug overdose as the underlying cause of cardiopulmonary arrest.

The percent of long-term and short-term survivors was very similar in comparing patients with cardiac disease, that subgroup with acute myocardial infarction and patients with non-cardiac disease (see Figure 3).

Figure 1.—The number of combined short-term and long-term survivors per year **(dotted line)** and the percent of the total number of patients per year **(solid line)** who were short-term and long-term survivors.

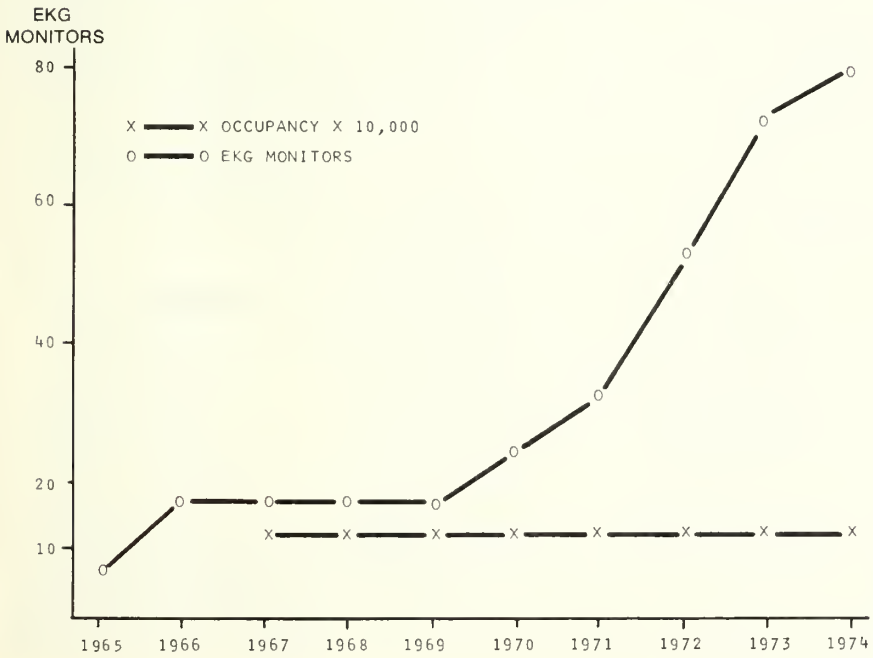

Figure 2.—Hospital occupancy and number of electrocardiographic (EKG) monitors (see discussion in text).

Location in Hospital

Figure 4 summarizes locations within the hospital where CPR was carried out. The years 1965 and 1966 were not included in this tabulation because the coronary care unit began operation in January 1967. The percentage of both long-term and combined long-term and short-term survivors was greatest in the emergency room.

Most of the CPR's were done where patient monitoring was available, such as in CCU, ICU or ER. Some nursing floor units, increasing in latter days of the study, had electrocardiographic monitoring capabilities, but those units are not separately identified.

CPR and Its Effects Upon In-Hospital Mortality

A long-term survivor is a patient who would have died during his hospital stay but was successfully resuscitated and able to be discharged due to successful resuscitation. The number of long-term survivors divided by the number of hospital deaths plus long-term survivors gives the index of the overall success rate of the resuscitation program, as shown:

$$\frac{\text{long term survivors}}{\text{hospital deaths plus long term survivors}} = \text{percent}$$

That number relates to the percent of patients who would otherwise have perished but instead were discharged from the hospital without evident neurologic or cardiopulmonary residua from their cardiopulmonary arrest. Those data are presented in Tables 2 and 3, summarizing data covering the total number of hospital and CCU patients.

An index of the application of CPR throughout the hospital is calculated by dividing the total CPR's by the sum of hospital deaths plus long-

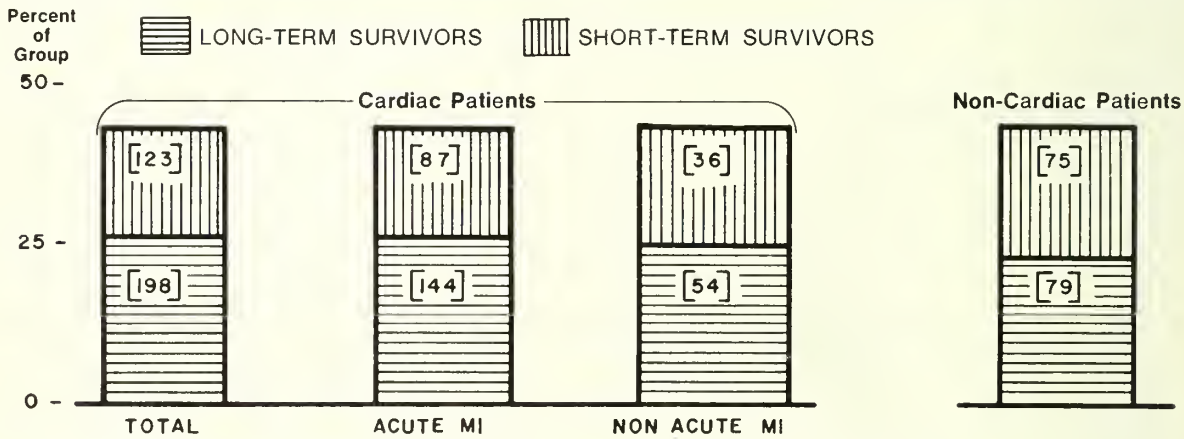

Figure 3.—Percentages of long-term and short-term survivors as they relate to the presence or absence of cardiac disease. Numbers in brackets represent total number of patients in that group (1965-1974).

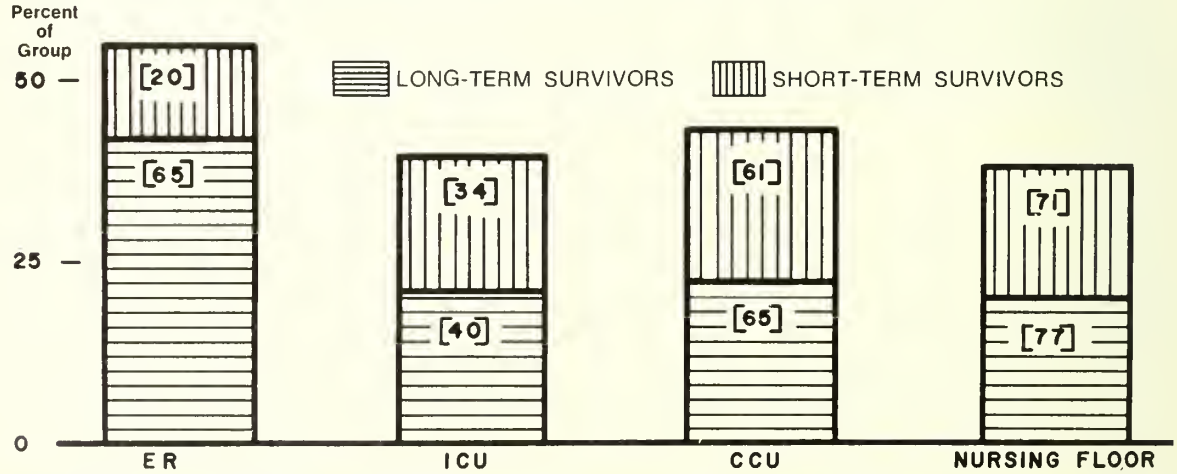

Figure 4.—Percentages of long-term and short-term survivors as they relate to patient location within hospital (1967-1974). Numbers of patients are in brackets.

term survivors. The total hospital ratio was 255/4333 or 5.9 percent, and in CCU 60/380 or 21 percent.

Discussion

St. Joseph Medical Center is located in the San Fernando Valley of California, an area in the northern portion of Los Angeles County. It serves primarily the adjacent residential communities. Some 80 percent of patients admitted to hospital lived in the San Fernando Valley and less than 1 percent lived outside the Los Angeles area.

There had been no pronounced change in the type of services offered nor patient population treated during the ten years of CPR data collection.

The average hospital stay of the total hospital patient population was 6.7 days. The cardiac patients, the largest single subgroup in CPR statistics, had an averaged stay of 9.4 days.

Of the total hospital patient population, 26 percent were 65 years of age, or older. Of the cardiac patients, 54 percent were at least 65 years of age. A negative relationship between increasing age and long-term survival has been previously published[8] and was confirmed in an earlier report[1] from this institution.

Cardiac patients accounted for about 9 percent of the total hospital patient population.

The tabulation of overall hospital CPR experience shows a trend toward increase in the annual number of CPR's as well as the percentage of long-term and short-term survivors (see Figure 1). Total hospital admissions did not increase notably and were not the basis for the increasing numbers. A full-time group of physicians trained in emergency medicine and covering the ER 24 hours a day began their services July 1, 1973, and, therefore, were only present during the last year and a half of the study. The increase in total CPR's as well as the percent of short-term and long-term survivors relates primarily to increasing training and experience of hospital personnel. This improvement in CPR programs with time has been previously reported.[13]

The increase in electrocardiographic monitors was likely a contributing factor to the progressive increase in CPR frequency and success (see Figure 2). The relationship is surely not linear and the optimal number of these monitors for a

TABLE 2.—*The Effect of Successful (Long-Term) CPR Performance on Overall Hospital Mortality*

	1967	*1968*	*1969*	*1970*	*1971*	*1972*	*1973*	*1974*	*1967-1974*
Occupancy (Patient Days/Year)	115,654	117,372	118,704	118,159	115,366	118,316	119,503	126,153	949,227
Deaths	563	603	630	427	499	436	442	478	4,078
CPR Long-Term Survivors	23	26	30	27	22	35	44	48	255
Deaths and CPR Long-Term Survivors	586	629	660	454	521	471	486	526	4,333
CPR Long-Term Survivors as a percent of Deaths and CPR Long-Term Survivors	4%	4%	5%	6%	4%	7%	9%	9%	5.9%

CPR = cardiopulmonary recuscitation

TABLE 3.—*The Effect of Successful (Long-Term) CPR Performance on CCU Mortality*

	1967	*1968*	*1969*	*1970*	*1971*	*1972*	*1973*	*1974*	*1967-1974*
Occupancy (Patient Days/Year)	1,612	1,721	1,871	1,992	2,471	2,436	2,340	2,564	17,007
Deaths	18	34	36	28	33	20	32	47	248
CPR Long-Term Survivors	10	9	9	8	4	7	10	9	66
Deaths and CPR Long-Term Survivors	28	43	45	36	37	27	42	56	314
CPR Long-Term Survivors as a Percent of Deaths and CPR Long-Term Survivors	36%	21%	20%	22%	11%	26%	24%	16%	21%

CCU = coronary care unit
CPR = cardiopulmonary recuscitation

successful CPR program cannot be presented. Theoretically it would be optimal to monitor every hospital patient from admission to discharge. The cost of such an approach in terms of personnel, equipment purchase and maintenance does not appear feasible at this time. Nevertheless, concentration of patients at higher than average risk of cardiopulmonary arrest in critical care (ICU/CCU/ER) nursing units is a logical alternative.

The number of CPR's decreased in the last two years of the study as the number of electrocardiographic monitors increased. This observation raises the question as to whether some cardiopulmonary arrests were prevented by recognition and early treatment of premonitory, dangerous arrhythmias.

Illness

Two thirds of patients undergoing CPR had cardiac disease and nearly half had acute myocardial infarction as the underlying basis for cardiopulmonary arrest. Because cardiac patients constitute a relatively small percentage of the total hospital population, selection of this group of patients for more intensive monitoring seems indicated. The type of monitoring indicated is outside the scope of this study. If acute cardiac arrhythmias are the primary basis for arrest, then electrocardiographic monitoring would be the technique of choice. This approach has been described previously.[14] Other techniques for monitoring critically ill patients, such as on-line arterial blood gas analysis, may be indicated in the future.[15,16]

The incidence of both short-term and long-term survivors is surprisingly similar when comparing cardiac patients, with or without acute myocardial infarction, and other patients. This observation came as a surprise. The basis for this pronounced similarity among diverse groups is uncertain.

Location in Hospital

Almost two thirds of CPR patients were being treated in the critical care areas (ICU/CCU/ER) at the time of the arrest. This group plus the electrocardiographic monitored patients in the specialized nursing care units account for over two thirds of CPR patients in the later years of this study. In other words, most of the patients destined to suffer a cardiopulmonary arrest had already been identified as requiring greater care than that available in a nonmonitored nursing unit. The other possibility—that patients who are not being monitored will less frequently receive needed CPR—cannot be rejected completely. Personal observations during the last five years of the study showed that acutely ill patients with cardiac disease were seldom in an unmonitored nursing unit.

The ER had the largest percent of long-term survivors, a testimony to the ER medical and nursing staff's abilities to successfully manage acutely ill patients.

CPR and Its Effect on In-Hospital Mortality

Evaluation of the success of a CPR program is difficult. The number of short-term and long-term survivors does not relate to total hospital admissions, discharges or occupancy. The populations served by various hospitals may be very dissimilar in age or underlying pathologic conditions.

The relation of short-term and long-term survivors to the total number of CPR patients is helpful in evaluating the CPR program. Those data are presented.

The ultimate goal of a CPR program is the hospital discharge in prearrest condition of patients who have died—that is, undergone a cardiopulmonary arrest. The number of long-term and short-term survivors reflects upon the successful implementation of a CPR procedure, but the successful discharge of a neurologically intact patient is what really counts.

If we assume that patients who have had a cardiopulmonary arrest would die in the absence of CPR, then the addition of the number of long-term survivors to the number of patient deaths would reflect the expected number of deaths in the absence of CPR.

If the figures presented represent an average hospital—and this writer has no way of speaking for or against that concept—then the number of hospital deaths would be 5.9 percent greater in the absence of CPR. This figure extrapolated to national or international levels is staggering.

The 21 percent success rate over eight years in the CCU is an even more impressive figure and is compatible with previous reports showing a pronounced decrease in mortality in patients with acute myocardial infarction since the inception of CCU's.

Conclusion

Ten years of in-hospital CPR experience is tabulated.

A technique for evaluating the impact of CPR on hospital mortality is presented. This technique is also applied to specific areas of the hospital.

The increasing magnitude and effectiveness of the CPR program over ten years is outlined.

The association between hospital location, electrocardiographic monitoring, patient illness and factors of long-term and short-term survival is considered. The lack of association between primary illness and long-term and short-term survival also is presented.

Patients at high risk, as shown by the necessity of CPR, are concentrated in critical care nursing units.

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Treatment of Corneal Herpes Simplex in Children

IN MY EXPERIENCE it has been far better to use ointment rather than drops in treating corneal herpes simplex in children. Remember, to put drops into the eyes of a struggling infant or youngster is almost impossible when the child is not cooperative. And of course if he is crying the drops are diluted immediately and washed out, so there really is little effect. You also have to be careful about drug application. I have seen a patient diagnosed as having a dendritic lesion of the cornea, a two-year-old child, and we prescribed doxuridane (IDU) ointment every four hours, five times a day. The patient was brought back two days later . . . and the lesion had enlarged. Well, either that patient was IDU-resistant or the drug was not getting in properly. I asked the mother, "How did you put the drug in?" And she took some ointment and squeezed it out onto her little finger and rubbed it into the upper lid. And I do not think that is an isolated instance.

—PETER R. LAIBSON, MD, *Philadelphia*
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Refer to: Davis JM: Food insurance and individual health accounts—A new approach to health care financing (Commentary). West J Med 129:518-520, Dec 1978

Food Insurance and Individual Health Accounts

A New Approach to Health Care Financing

JAY M. DAVIS, MD, PhD, *Arcata, California*

HEALTH INSURANCE—national or otherwise—is no answer to rising costs of health care. It cannot solve the problem. Because, to a large extent, it *is* the problem.

The continuing rise in medical costs is directly traceable to the rise in health insurance—to the rise in third-party payments. This should come as no surprise. After all, if two persons enter into a contract for services, but a third person foots the bill, neither the provider nor the recipient will attempt to control costs. And this is precisely what happens in today's "health market." Why not spend a few extra days in the hospital recuperating, why not have that plastic surgery done? Why not do a CT scan, or colonoscopy or triple-vessel bypass? After all, as the sweet refrain goes, "the insurance pays for it."

Health insurance has failed because modern health care is not an insurable item. To put this into proper perspective, consider life insurance. A person buying life insurance pays regular premiums so that when he dies his beneficiaries will be compensated. The system works because people are not in a rush to collect their benefits.

Hunger Insurance

By contrast, let us invent hunger insurance. With such a plan, a person would pay a fixed premium to insure against hunger. Then, if he became hungry, he could take his policy to any supermarket where he would be entitled to the necessary food to relieve his hunger.

One can easily imagine the situation that would develop. Checkout lines would become clogged as clerks read policies to find if steak and lobster were covered. With nobody paying cash, bookkeeping and billing departments would have to be established. Increased paperwork would mean increased staff which would mean increased prices.

And with price no object, people would demand fancier markets and fancier foods. Modern technology would be quickly applied as markets competed for the food insurance dollars. "Food care specialists" and other ancillary personnel would be trained to enhance the "supermarket experience." Expensive prepared delicacies would abound and replace simple meat and potatoes. Soon, gastronomic profiles might be run on each client to see which foods were most appropriate for him, and computerized printouts could guide his selection of foods. To let a patron walk the aisles of a market without such a diagnostic workup would be gastronomic malpractice.

The cost of these developments would be staggering. Food prices would rise precipitously. But patrons would not have to worry: their insurance would pay the bills.

Alas, health insurance is much closer to food insurance than to life insurance. And that is precisely why it does not work. *Insurance is workable only to the extent that the insured event is an undesirable one.*

Life insurance works because people do not want to die. Food insurance would not work because people love to eat. And health insurance stopped working when people lost their fear of doctors.

The failure of private health insurance is evident from the skyrocketing cost of premiums. The failure of federal programs is seen in massive cost

Reprint requests to: Jay M. Davis, MD, PhD, Arcata Family Medical Group, Inc., Arcata Family Health Center, 4555 Valley West Boulevard, Arcata, CA 95521.

overruns and the near bankruptcy of the Social Security System.

The response of private insurance companies has been to urge doctors and patients to curb their spending of insurance dollars. The government response has been more predictable: more agencies and more bureaucracy. We have PSRO, HSA and battalions of new bureaucrats—all of which simply add more paper and payroll to the swollen costs.

Yet all these efforts are doomed to fail because they ignore the fundamental problem: neither the provider not the recipient is motivated to watch expenses. Any system of health care that fails to provide an incentive for such cost control is bound to be unnecessarily expensive.

Suffice it to say that I think there is a better way. Let me present it briefly.

Individual Health Accounts

The basic concept is the Individual Health Account (IHA). Into this account a person makes monthly payments—just as he does today with his health insurance. However, the money remains *his,* and he receives a quarterly accounting from the insurance company. Moreover, when he dies, the funds are part of the inheritance he leaves. But I am getting ahead of myself.

When a person goes to a doctor, emergency room or hospital, he takes his passbook with him, and pays his bill with the appropriate "check" drawn against his account.

There is a maximum amount of money required in each IHA, depending on the person's age, sex, dependents and other statistical risk factors. This would be a sizable sum to provide a cushion against likely expenses. With such a cushion patients would not hesitate to seek the care they really need. However, after this maximum is reached, any overflow is paid directly to the individual person. He may spend this overflow money any way he wishes (not necessarily on health care). In this fashion, a real incentive is provided for cost control.

Therefore, a patient needing renal dialysis is likely to choose home dialysis at $3,000 a year rather than spending $12,000 to go to a dialysis center. (After $3 billion has been spent, the government is still "looking into" the possibility of home dialysis payment under Medicare.) Or, an octogenarian who "could benefit" from a bypass operation may instead decide to leave that $10,000 to his grandchildren. And finally, an outpatient may one day ask, "Do I really need that CT scan or skull series just because I have this headache?"

As patients begin to see how their health care funds are being spent they will begin to assert some control over them. Like shoppers in supermarkets, they will begin looking at prices and deciding what is necessary and what is not. Obviously, they will need advice from their doctors to make these choices, but if they do not like the advice they get from one physician they may well check with another.

An advantage of this system is that patients will no longer have to read the fine print on their insurance contracts. If they wish to visit an emergency room at midnight for a rash that has persisted for four months, they will simply have to pay the consequences—out of their IHA. Similarly, the distinction between elevation of a bladder (acceptable) and elevation of a breast (currently unacceptable) would disappear. The hand that controls the purse would control the decision. And that hand would belong to the patient.

But what about patients who are not working and do not contribute to an IHA? What about a welfare patient covered by Medicaid? This segment of population consumes enormous amounts of health care.

Obviously the state could put funds into an IHA for indigents. But would it be reasonable for such patients to keep the overflow of money when they did not put that money in? And if they cannot keep the excess would they be motivated to spend carefully?

State Health System

As an alternative, all persons without an IHA would be assigned to the State Health System (SHS). Such patients would be randomly assigned to a physician. The designated physician would receive a monthly fee for taking care of that patient and would be responsible for all his expenses. Consequently, if such a patient needs a week in the hospital, or a triple bypass, or CT scan, it is the physician who foots the bill. And, if the physician does not feel that a particular headache warrants a CT scan and a neurological consultant, it is not done—unless the patient wishes to pay for these services himself.

If a patient is not satisfied with the service he is receiving from his physician, he is free to

change doctors. As soon as he does so, the stipend is transferred from his old to his new physician. Therefore, a physician who fails to satisfy his State Health patients will lose them then as surely as he will lose his private (IHA) patients. In this sense, there will be a single standard of care; and patients will be the final determinant of where their health dollars go.

The monthly fee paid to a physician would reflect the patient's age, sex, dependents and those other variables known to affect his risk. To get physicians to participate, these fees would have to reflect current economic realities. Any physician taking part in the program would have to accept all patients assigned to him (that is, he could not refuse patients who were sick and likely to be costly). This State Health System, of course, is nothing more than a Health Maintenance Organization.

A Two-Tier Health Plan

What I am suggesting, then, is a two-tier health plan. In one case, the IHA, it is the patient who is given charge of his finances. He receives the services, and he decides where and how his money will be spent. He is rewarded for careful spending, and the surplus is his. Most people would be covered with IHA's.

But, for those persons without an Individual Health Account, the cost is paid by the state. But the control is not exercised at a distance by people with only a vague knowledge of the particular patient-doctor interaction. Rather it is the provider who is made responsible for the patient-care costs. This removes some of the prerogatives from a patient—but he has already been totally freed of any financial responsibility. And he still retains the freedom to switch doctors.

In both cases, the cost control is exercised at the point where costs are initiated: the patient-doctor interface. *This is crucial.* We have repeatedly seen how ineffective it is to try to control costs from a distance. Only when the costs are controlled by either the provider or the recipient (not some distant bureaucrat) will the costs of care become affordable.

A few additional points bear mentioning. First, a person is not locked into one aspect of the system or the other. A person who exhausts his IHA is immediately transferred to the State Health System. Similarly, a person can always switch back to the Individual Health Account system as soon as he is contributing. But he is *always* under one system or the other. Never again will there be a third party arrangement where neither the recipient of the services nor the provider of the services is responsible for the costs.

Second, physicians covering State Health patients would undoubtedly need some kind of catastrophic health coverage to provide for those rare patients with staggering but necessary expenses. A 20-day coma or multisurgery accident victim could easily bankrupt a physician. Hence, a limit would have to be set on the provider's financial liability.

Finally, consider the administrative cost of such a system. Gone would be the hordes of insurance forms, billing clerks and claims committees. Absent would be Medicaid stickers, emergency authorizations and interminable correspondence to find out what is covered under various policies or rules. The money saved in this streamlining would be phenomenal. No longer would 25 percent to 50 percent of every health dollar go for administration. Health care dollars would be spent on health care.

I have described what I consider an alternative for health insurance. It keeps the cost control in the hands of the doctor and patient. It is a blueprint for a workable system of universal health care without the nightmare of third parties.

CLINICAL NOTES IN DIAGNOSTIC CARDIOLOGY

Refer to: Cabeen WR Jr, Roberts NK, Child JS: Recognition of the Wenckebach phenomenon (Clinical Notes in Diagnostic Cardiology). West J Med 129:521-526, Dec 1978

Recognition of the Wenckebach Phenomenon

WILLIAM R. CABEEN, JR., MD
NIGEL K. ROBERTS, MD
JOHN S. CHILD, MD
Los Angeles

ATRIOVENTRICULAR (AV) nodal Wenckebach conduction is a common clinical occurrence, frequently associated with acute inferior infarction or increased vagal tone, which is easily recognized by clinicians[1] (Figure 1).

The Wenckebach phenomenon, however, represents a conduction abnormality that can occur at many other levels in the cardiac conduction system (see Table 1 in Summary section), a fact that is less well appreciated, frequently resulting in its lack of recognition at those other levels. In addition to allowing the satisfaction of a proper electrocardiographic diagnosis, realization of the presence of the Wenckebach phenomenon, a type of abnormal, depressed conduction, shows the existence of a conduction abnormality at that level and therefore allows for more accurate prognostication and appropriate treatment. The treatment required, or the effect of documentation of an abnormality of conduction will depend on the location of the abnormality and whether or not it results in symptoms.

Several case examples will be presented which illustrate the Wenckebach phenomenon at levels other than the AV node during antegrade conduction to allow discussion of the general features of the Wenckebach structure that permit its recognition wherever it occurs.

CASE 1. The patient is a 56-year-old man with a three-year history of mild exertional angina pectoris. An episode of severe substernal chest pain occurred associated with nausea and lightheadedness, and the patient was admitted to the Cardiac Care Unit, University of California, Los Angeles, School of Medicine. Serial electrocardiograms and enzymes documented the evolution of an acute inferior myocardial infarction. On the second day of his hospital stay, an irregular atrial rhythm (Figure 2) was noted, characterized by grouped beating with progressively shorter PP intervals followed by a pause and a repeat of the pattern; thereby showing sinoatrial Wenckebach block[2] (see discussion). This was followed by approximately 24 hours of sinus bradycardia (rate 50 beats per minute) and then by a return to normal sinus rhythm.

CASE 2. A 73-year-old man had a long history of coronary artery disease and had had two previous myocardial infarctions followed by typical exertional angina for several years. He was admitted after a severe bout of chest pain and was found to have an acute anterior myocardial infarction. Two days later an accelerated idioventricular rhythm developed with retrograde conduction to the atria (Figure 3). The retrograde VA (ventriculoatrial) conduction occurred with the Wenckebach structure resulting in (1) progressively longer conduction times (R-P intervals) until conduction failed (resulting in a pause in atrial rhythm—Figure 3 right) or (2) progressively longer conduction times until the P wave was delayed enough to allow return to the ventricles—a reciprocal beat—and subsequent repeat of this cycle (Figure 3, left).

CASE 3. A 72-year-old Oriental woman was admitted to the psychiatric service for treatment of depression. She had a previous history of premature ventricular contractions which had been treated with quinidine in the past. Although there had been no clinical history of chest pain or infarction, a 12-lead electrocardiogram showed a QS pattern in leads V_1 to V_3 suggesting probable previous anteroseptal myocardial infarction. Because of this finding, it was felt likely that the previous ventricular ectopy was due to arteriosclerotic cardiovascular disease. As part of the treatment for depression, therapy was begun with imipramine, a tricyclic antidepressant. The pa-

From the Departments of Medicine and Pediatrics, Division of Cardiology, University of California, Los Angeles, Center for the Health Sciences.

Reprint requests to: William R. Cabeen, Jr., MD, Division of Cardiology, Department of Medicine, UCLA School of Medicine, Los Angeles, CA 90024.

tient was subsequently noted to have an irregular cardiac rhythm and a 24-hour Holter electrocardiogram monitor was done, a portion of which is presented in Figure 4. It shows sinus rhythm with ventricular extrasystoles occurring in an alternating bigeminal and trigeminal pattern. Note that each successive QRS of supraventricular origin is followed by a ventricular premature complex. The *coupling interval increases* until a supraventricular QRS fails to be followed by a ventricular beat and that this cycle repeats resulting in the alternation between "bigeminy" and "trigeminy." If these ventricular beats are due to ventricular reentry (the mechanism most commonly felt to be responsible for premature ventricular contractions), the progressively longer conduction time (coupling interval) followed by failure of conduction (failure of ventricular complex to appear after a supraventricular complex) suggests Wenckebach conduction in the reentry loop (see Figure 4 and discussion).[3] If the ventricular beats are due to an ectopic (but not parasystolic) ventricular focus, the progressive increase in coupling interval followed by failure of appearance of a ventricular beat also suggests the Wenckebach phenomenon—that is, Wenckebach exit block from that ectopic focus.[4]

Discussion

The Wenckebach phenomenon represents an abnormality in conduction of the cardiac impulse from one area of the heart across a conduction path to another area. Its occurrence during conduction across the AV node is the form with which most clinicians are well acquainted and is that first described by Wenckebach from inspection of pulse tracings.[1]

When typical antegrade AV Wenckebach conduction occurs one is alerted on electrocardiograms by the failure of a P wave to conduct to the ventricles. On subsequent analysis, one finds the features that lead to the diagnosis of the Wenckebach mechanism as a cause. When Wenckebach conduction occurs at a different level, these same features are present and once recognized will allow one to diagnose the Wenckebach phenomenon there as well. These features include:

1. *Progressive conduction delay* from the proximal area across conduction tissue to the distal area until conduction fails resulting in a pause before repeat of this cycle. In the case of AV Wenckebach conduction, there is progressive delay in conduction from the atria (proximal area) across the AV node (the conduction path) to the ventricles (the distal area) manifesting as progressive PR prolongation. Therefore, as illustrated diagramatically in Figure 1, the PR goes from 15 (hundredths of a second) to 35, to 45 to 50 until the P wave fails to conduct.

2. Progressive *decrease in the increment of delay* through the cycle. In typical AV Wenckebach conduction, although each PR is longer than the preceding one (as above), the amount by which it is longer—the increment—decreases. This is indicated in Figure 1 below where the successive increments are 20 (35 minus 15), 10 (45 minus 35) and 5 (50 minus 45).

3. Progressive *shortening of activation intervals* followed by a pause. This is a direct result of feature 2. The distal area is activated at shorter

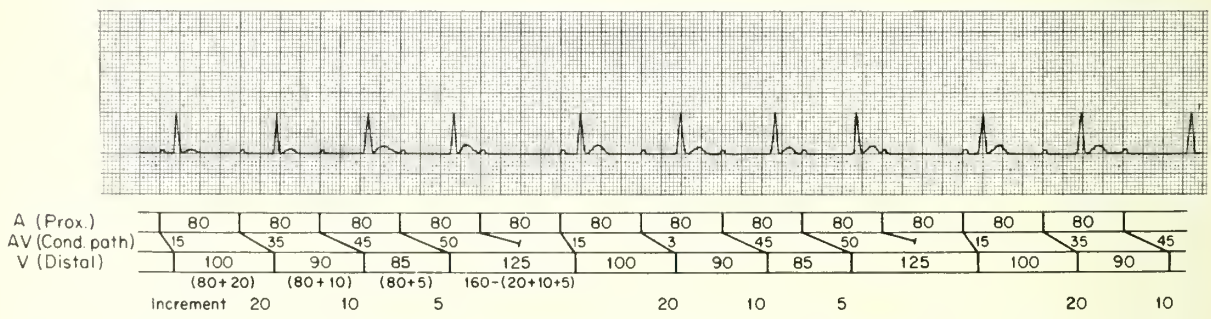

Figure 1.—Diagramatic Representation of Atrioventricular Nodal Wenckebach **Upper:** Electrocardiographic appearance, **Lower:** Ladder diagram. Note (1) constant atrial cycle length (80) indicated in the ladder diagram at the atrial level A; (2) progressive AV conduction delay indicated in the ladder diagram at the atrioventricular AV with progressive **decrease in increment** of increase; (3) progressive decrease in ventricular cycle length (RR interval) indicated in the ladder diagram at the ventricular level V, and (4) pauses in ventricular rhythm which are less than twice the basic atrial cycle length. (All intervals are indicated in hundredths of a second.) The ladder diagram is also illustrative of Wenckebach when it occurs at other levels with the corresponding proximal area, conduction path and distal area indicated in parentheses at the left.

and shorter intervals until there is failure of activation and a pause. In AV Wenckebach conduction this manifests as progressive shortening of the RR interval. Note in Figure 1, the RR is 100, 90, 85 then 125 (pause) and repeat. As each impulse is conducted, its arrival in the distal area is delayed so that the cycle length in the distal area is longer than the cycle length in the proximal area (RR is longer than PP). However, because of feature 2 above, the amount the arrival is delayed, compared to arrival of the previous impulse, decreases (the increment decreases) therefore each subsequent activation interval (RR in AV Wenckebach) is shorter than the one preceding it and therefore the activation intervals shorten. Thus, the rate of the distal area appears to accelerate during each cycle.

4. The pause is *less than twice the cycle length* of the proximal or distal area. The pause due to failure of conduction from proximal to distal area is reduced by the amount of the increments of delay preceding it. In AV Wenckebach (Figure 1) the pause is less than twice the PP or any RR of the cycle. It is twice the PP (160) minus the sum of the increments ($160-[20+10+5]=125$).

When the Wenckebach phenomenon occurs during conduction other than antegrade through the AV node, as in Figure 1, one finds the same features but because it is occurring in another area, the effect on various portions of the electrocardiogram will be different (such as PP, RR, PR, and so forth). Note that the ladder diagram in Figure 1 indicating atrial activity (A); AV conduction (AV), and ventricular activity (V) can also be used to illustrate Wenckebach conduction structure at any other level. The proximal area corresponds to the atrium, the conduction path to the AV node and the distal area to the ventricles in this diagram (indicated in parentheses at the left of the ladder diagram in Figure 1).

When the Wenckebach phenomenon occurs during conduction from the sinus node (proximal area) across the sinoatrial junctional tissue (conduction path) to the atria (distal area) one has so-called SA (sinoatrial) Wenckebach block as in case 1 (Figure 2). Activity of the sinus node and SA conduction intervals are not manifest on the surface electrocardiogram, but progressive shortening of the PP interval followed by a pause less than twice any PP interval shows the features of and allows the diagnosis of the Wenckebach phenomenon.[2] This structure is indicated by the ladder diagram below in Figure 2. The Wenckebach structure and, therefore, the ladder diagram is the same as in AV Wenckebach (Figure 1) except that the anatomical levels indicated by the ladder diagram differ. The postulated sinus firing and sinoatrial conduction cannot be directly seen on the surface tracing but the atrial activity, typical of the distal area in the Wenckebach structure shows its presence. Because the patient had manifest SA Wenckebach conduction as illustrated here, it is likely that the period of sinus bradycardia that occurred transiently (not illustrated) was due to 2:1 SA block, especially in view of the fact that the rate of the bradycardia was approximately half the earlier manifest sinus rate as in Figure 2.

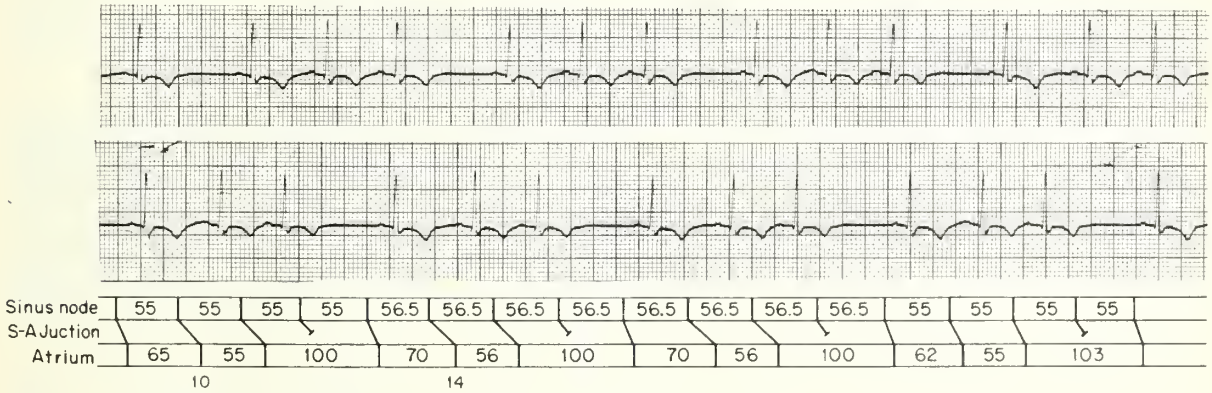

Figure 2.—Sinoatrial Wenckebach. Note decrease in PP interval (65 to 55, and so forth) followed by a pause less than twice any PP interval; features of the distal area in the Wenckebach phenomenon. Note also the similarity of the ladder diagram here with that in Figure 1 except that here the atrium is the distal area and thus is indicated in the lower level of the ladder diagram. The diagramed sinus and sinoatrial junction activity in the ladder diagram is inferred as activity of these areas is not directly recorded on the surface electrocardiogram. (Intervals are indicated in hundredths of a second.)

It should be pointed out that SA Wenckebach conduction can be thought of as a form of exit block—that is, SA exit block. When other foci dominate the cardiac rhythm (such as atrial, junctional or ventricular ectopic rhythms) the Wenckebach phenomenon can occur during exit of the impulse from such ectopic foci. Again the manifestation will be that of the distal area in the Wenckebach structure—that is, progressive decrease in activation interval, followed by a pause and repeat. Similarly the structure can be illustrated by a laddergram such as Figure 1 with the "proximal area" corresponding to the actual ectopic focus, the "conduction path" to the exit pathway and the distal area to the activation of the locale of the focus (such as atrium, junction or ventricle). Again, the activity of the proximal area (the ectopic focus itself) and the conduction path will not be seen on the surface electrocardiogram but the behavior of the distal area (atrial, junctional or ventricular) activation shows the features of and allows the diagnosis of the Wenckebach phenomenon.

In case 2, by analyzing the ventricular and atrial activity and their relationship one again recognizes the Wenckebach structure, but in this case it occurs during retrograde AV conduction from the ventricles (the proximal area related to the direction of progression of the impulse) across the AV node (the conduction path) to the atria (the distal area, again with respect to the direction of travel of the impulse). This case has the additional feature of return activation of the ventricles, an echo beat (the narrowed QRS's), when the atrial activation is late enough with respect to the previous QRS. One can see, then, in the ladder diagram in Figure 3 the following:

- Progressive conduction delay retrogradely across the AV node, that is, progressive increase in R-P interval from 10 to 30 to 37,
- Progressive decrease in increment of delay from 18 to 5 resulting in
- Progressive shortening of activation intervals —that is, PP intervals—and then,
- A pause in activity (atrial) less than twice the basic cycle length.

Again, one discovers the components of and thereby diagnoses the Wenckebach phenomenon.

In case 3 (Figure 4) careful inspection also will show such components, but because the structure is at a different level the manifestations will be different. Note in Figure 4 that each sinus conducted QRS is followed by ventricular premature complex (bigeminy) but with an *increasing coupling interval* until appearance of the premature fails and the cycle repeats resulting in alteration between bigeminy and trigeminy. The presence of this progressively increasing interval (coupling interval), then failure of appearance followed by a repeat of the cycle, again, is a feature of the Wenckebach structure and shows its presence. The ladder diagram in Figure 4 shows the complete structure with the Wenckebach phenomenon taking place within the reentry loop probably responsible for the bigeminal appearance of the ventricular beats. If, on the other hand, the extrasystoles are due to an ectopic ventricular focus, rather than reentry, the Wenckebach phenomenon is still suggested by the behavior of the coupling interval and alteration between bigeminy and trigeminy. This would occur when the discharge of the ectopic focus is coupled to the

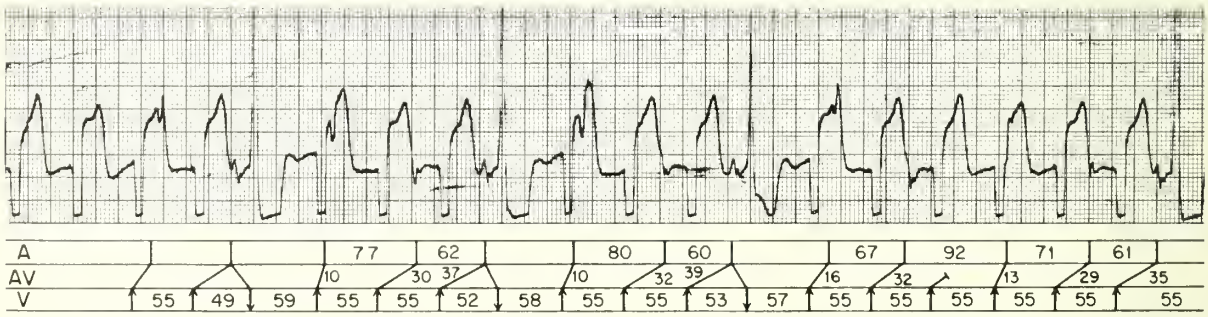

Figure 3.—Retrograde Atrioventricular (AV) Wenckebach. Note as illustrated diagramatically in the ladder diagram: (1) progressive retrograde conduction delay across the AV node (R-P increases from 10 to 30 to 37 hundredths of a second on the left); (2) progressive decrease in increment of delay; (3) progressive shortening of atrial activation intervals—that is, PP interval; (4) pause in atrial activity (on right) less than twice the basic cycle length.

sinus conducted QRS's (that is, it is not parasystolic, see below). Therefore, each sinus conducted ventricular depolarization sets the stage for ventricular ectopic discharge but when this occurs exit conduction shows the Wenckebach phenomenon resulting in the observed increasing coupling interval followed by exit block and thus failure of an ectopic beat to appear.[4] (A parasystolic ectopic focus can also show Wenckebach exit block but in that case the relationship to the basic sinus rhythm is not constant or repetitive as in this case. With parasystolic focus Wenckebach exit block, the same features outlined for Wenckebach conduction apply in addition to those of the parasystolic focus itself. Therefore, the interectopic interval within a Wenckebach cycle is not constant but progressively shortens [feature 3, above] and the ectopics have a random relationship to the underlying sinus rhythm).

Atypical Wenckebach

Rhythms that manifest all the features outlined above show so-called "typical" Wenckebach phenomenon. If many *but not all* of these features are found, then atypical Wenckebach phenomenon is said to be present. This variation has been most completely evaluated for antegrade AV nodal Wenckebach conduction and in fact has been found to be probably more common than typical Wenckebach conduction in that situation.[6] The failure to show all the features described is due to inconsistent change in the conduction delay. In typical Wenckebach conduction, as each impulse is conducted, it is progressively delayed, but with a progressive decrease in the increment (amount of increase) of that delay as described above. In atypical Wenckebach conduction, instead of decreasing, the increment may increase, may fail to decrease (that is, stay the same) or there may be a negative increment (that is, one conduction interval may actually be less than one preceeding it). This, of course, will disturb the behavior of the conduction delay and the resultant activation intervals of the distal area. Therefore, the features described previously may not all be present. Thus, in atypical Wenckebach there may not be *progressive* conduction delay, although delay will tend to increase through the cycle as a whole and there may not be progressive shortening of activation intervals, although the last activation interval is usually less than the first of a cycle; and the pause remains less than twice the cycle length of the proximal or distal area. For AV Wenckebach conduction atypical forms show one or more of the following: (1) last increment increased from previous increment, (2) last increment the largest increment, (3) PR interval repeated during the cycle (increment = 0), (4) PR interval decreased at least once during the cycle (negative increment) or (5) first increment not the largest increment of the cycle.[6] Also for AV Wenckebach conduction it has been shown that the frequency of atypical Wenckebach conduction increases as the AV conduction ratio increases and that at conduction ratios greater than 6:5 AV conduction is almost always atypical.[6] Because one has both proximal and distal area behavior to evaluate in AV Wenckebach conduction its recognition is still possible when atypical. When atypical Wenckebach conduction occurs in other areas where only the distal area activity is observable, recognition of the Wenckebach phenomenon may be difficult or impossible.

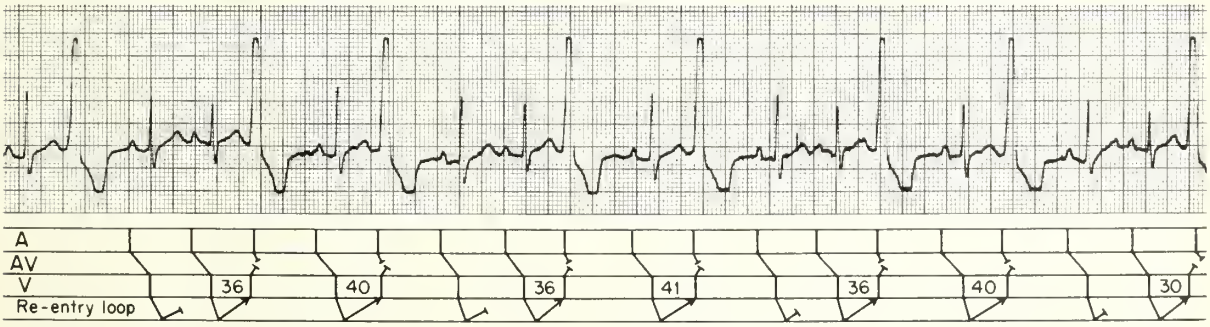

Figure 4.—Reentry loop Wenckebach. Note alternation between bigeminal and trigeminal patterns. This is due to the failure of completion of reentry due to Wenckebach block in the reentry path. This is shown by progressive increase in conduction delay (coupling interval), for example, from 36 to 40 (hundredths of a second) followed by a failure of completion of the loop and appearance of a ventricular complex; then repeat of the cycle.

TABLE 1.—*Sites of Conduction*

Atrioventricular (AV) conduction
Ventriculoatrial (VA) conduction
Sinoatrial (SA) conduction[2]
Bundle branch conduction[5]
Ectopic pacemaker exit[4]
Reentry pathway conduction[3]

TABLE 2.—*Wenckebach Phenomenon Clues*

Group beating
Progressive conduction delays followed by a pause
Progressive shortening of activation intervals followed by a pause

TABLE 3.—*Manifestations of Wenckebach Phenomenon*

AV Wenckebach[1]
Progressive PR prolongation
Decreasing increment of PR increase
Progressive shortening of RR interval followed by a pause
VA Wenckebach[1]
Progressive R-P prolongation
Decreasing increment of R-P increase
Progressive shortening of PP interval followed by a pause
Pause less than twice RR
SA Wenckebach[2]
Progressive PP shortening followed by a pause less than twice any PP interval
Bundle Branch Wenckebach[5]
Progressive increase in QRS duration to a maximum, then return to normal duration and repeat of the cycle
Ectopic Exit Wenckebach[4]
Progressive increase in expected appearance time followed by failure of appearance of an ectopic complex, then repeat
Reentry Path Wenckebach[3]
Progressive increase in appearance of reentrant complex followed by failure of reentry to occur then repeat of cycle

Prognosis and Therapy

The recognition of the Wenckebach phenomenon localizes the presence of conduction disease at the level of the conduction path involved. The prognostic significance and therapy required will depend on the level at which this is occurring, whether symptoms result from the intermittent failure of conduction and the significance that progression to complete block at that level might have. Drugs would subsequently be chosen based on the desirability or need to improve or worsen the conduction at that level. For example, progression to complete AV or SA block (or bundle branch block when the contralateral bundle branch is also diseased) would result in severe bradycardia or asystole due to complete heart block or failure of appearance of sinus rhythm. Therefore, the use of drugs which could further depress conduction (such as digitalis, lidocaine, quinidine and the like) might be contraindicated. Depending on the setting in which it was occurring and whether there were resultant symptoms, a pacemaker might be considered. On the other hand, Wenckebach conduction in a reentry pathway or ectopic focus exit pathway might lead to the choice of drugs that depress conduction there further in order to prevent the appearance of the resultant arrhythmia.

Summary

The Wenckebach phenomenon can occur during conduction at almost any level in the heart, Table 1.

When this phenomenon occurs, careful analysis of the tracing will show the features described and allow proper diagnosis. Clues to the presence of this group of features (Table 2) should lead one to such careful analysis.

When typical Wenckebach conduction occurs at each of the levels shown in Table 1, the manifestations will be as outlined in Table 3.

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Refer to: Pappagianis D, Einstein H: Tempest from Tehachapi takes toll or Coccidioides conveyed aloft and afar (Medical Information). West J Med 129:527-530, Dec 1978

Tempest From Tehachapi Takes Toll or Coccidioides Conveyed Aloft and Afar

DEMOSTHENES PAPPAGIANIS, MD, PhD, *Davis, California, and*
HANS EINSTEIN, MD, *Los Angeles*

New cases of acute primary coccidioidomycosis in large numbers resulted from a windstorm that blew through Kern County, California, on December 20, 1977. In most of these cases clinically apparent infections developed in early and mid-January 1978 and occurred not only in persons exposed directly to the dust raised by the windstorm but also among those in many areas to the north and west of Kern County. The exposure to the dustborne Coccidioides immitis was brief because of the arrival of drenching rains, but the continued heavy rainfall increased the potential for large numbers of cases of coccidioidomycosis to occur in the summer-fall season.

To the exports from Bakersfield, California, and environs—oil, livestock, cotton, potatoes, grapes, Merle Haggard, Buck Owens—can be added one of dubious value, coccidioidomycosis. During the first five months of 1978 a remarkable number of new cases of acute primary coccidioidomycosis were recognized in California. These resulted from the dust storm that blew through Kern County on December 20, 1977, depositing tremendous amounts of soil and arthrospores of Coccidioides immitis to the north and west of this southern-most county of the San Joaquin Valley. The heavy deposit of windblown dirt in Kern County was phenomenal. One resident described the deposition of dirt in her swimming pool as resembling "the result of a Fleet's enema." These winds in Kern County provided fallout of soil in the northern and coastal areas of San Francisco, Marin County, Sacramento, the east bay, and Santa Clara and Monterey counties, cities in the northern Sacramento Valley, and as far north as Oregon.

The northern areas were not directly affected by the ground level windstorm that had struck Kern county but the dust was lifted to several thousand feet elevation and, borne on high currents, the soil and arthrospores along with some moisture were gently deposited on sidewalks and automobiles as "a mud storm" that vexed the residents of much of California. The dust storm climaxed a year of drought in California that interestingly, besides its desiccation of the state, had also been accompanied by the lowest number (375) of reported cases of coccidioidomycosis in recent years.

The first illnesses of the new outbreak became apparent in late December. January 1, 1978, was the date on which symptoms that were serologically confirmed—in our laboratory at University of California, Davis (UCD)—developed in the maximum number of cases (22); this was 12 days after the dust storm. In the ensuing days there was a sustained incidence of new cases, for example, 18 cases on January 5 and 17 cases on January 10—16 and 21 days, respectively, after the dust

From the Department of Medical Microbiology, University of California, Davis, School of Medicine, and the Barlow Hospital-University of Southern California, Los Angeles.

Submitted July 10, 1978.

Reprint requests to: Demosthenes Pappagianis, MD, Dept. of Medical Microbiology, University of California, Davis, School of Medicine, Davis, CA 95616.

storm. After this the number of new cases began to fall off to 1 or 2 cases per day to yield a total of 216 cases (10 with onset of symptoms in December) through the end of January. Most of these detected at UCD were drawn from nonendemic areas of Northern California.

In Kern County 98 new cases were detected in January 1978 and 36 in February, compared with 3 and 14 cases, respectively, for these months in 1977. New cases had fallen off by March, eight being recorded compared with five in March 1977.

Cases of coccidioidomycosis with onset of symptoms in January but with belated diagnosis were still being diagnosed serologically or by culture late into May.* By the end of the first 12 weeks of 1978, a total of 379 new cases of coccidioidomycosis resulting from the dust storm were confirmed serologically at UCD, most from nonendemic areas of Northern California, and 142 were noted in Kern County. At this time, 359 new cases had been reported to the California State Department of Health (CSDH). These figures can be compared with the totals reported to the CSDH for the years 1977 (375), 1976 (500), 1975 (442) and 1974 (526). By the end of May the number (greater than 532) reported had exceeded those in any previously reported entire year in California.

Because of imperfect reporting to the County or State Health Departments, the tallies will be incomplete. At UCD we have detected 116 dust storm-related infections in Sacramento, 15 in Salinas and 51 in Stockton, but we realize that these and the 7 from San Francisco and 10 in Oakland represent incomplete figures.

The fiscal impact of coccidioidomycosis can only be crudely and incompletely estimated. Based on two studies[1,3] an *average* hospital stay for each case of coccidioidomycosis was placed at 35 days. Assuming $100 per day for hospital room costs, the 521 new cases recognized through UCD and in Kern county during the first three months of the year would have accounted for expenses of $1,823,500 for room costs alone. The seasonal recurrence of coccidioidomycosis in the southwestern United States (more than 500 cases per year are reported in Arizona) requires, therefore, a continuing substantial medical expenditure.

Additional cases in other species (canines and nonhuman primates) resulting from the dust storm were recognized in customarily nonendemic areas (for example, a gorilla in the San Francisco Zoo died from the effect of infection and attempted therapy).

The question whether the deposition of arthrospores by the dust storm in nonendemic sites, in northern and coastal areas, will have established new endemic foci will be answered by findings in the summer coccidioidal season or seasons. Inasmuch as small foci of endemicity in inland Northern California have been recognized,[17] it is conceivable that these regions could become more broadly endemic. Whether the regular agricultural tillage and cultivation of these areas and the particular circumstances of weather (rainfall is normally much heavier in the Sacramento Valley than in the recognized coccidioidal areas of the San Joaquin Valley), enhance a competitive microflora of the soil that may inhibit proliferation of C. immitis remains to be seen. It is not likely that Marin County, San Francisco, Oakland, Salinas and Monterey will provide hospitable circumstances for C. immitis to grow and persist. The near coastal area of Pacific Beach (San Diego County) did provide a source of coccidioidal infection[7] but the more northern coastal areas probably provide sufficiently different weather and soil to avert permanent establishment of C. immitis. (While Pacific Beach appeared to be the closest to a contemporary marine environment harboring C. immitis, recently a sea otter infected with C. immitis was found at Morro Bay, San Luis Obispo County [Kent Osborn—personal communication]; and the Swateks[16] have reported on the growth of C immitis in a medium containing sea water.)

The confinement of onset of new cases essentially to the end of December and the month of January was a fortunate result of the advent of the drought-ending rains. In Northern California this occurred on December 21 in the San Francisco Bay Area. In Sacramento, there were 0.45 inches of rain on December 21 and 1.10 inches on December 22. Usually such rains arrive in November or early December to end the annual increase in cases of coccidioidomycosis occurring in California during the late summer and fall. The latter was depicted clearly by Smith in his studies of Valley Fever in the 1930's and during World War II.[10,11] Small numbers of cases of acute coccidioidomycosis are encountered throughout the year both in California[10,11] and

*Sharon Beall, Sue Lindsey and Mary Toulson of UCD, and Jack Leonard of Kern County shared the burden of the tremendous increase in serologic testing.

in Arizona.[1,9] Interestingly, Arizona which has (in its coccidioidal endemic areas) less rainfall than California, has a short period of decreased cases of coccidioidomycosis in humans immediately following the summer rain showers, but seems to lack the pronounced diminution of cases during the winter months that characterizes California. Canine coccidioidomycosis is increased in Arizona during the winter months[8] possibly as a result of increased digging in soil by dogs during the cooler months of the year.

The immediate consequence of the rain following the dust storm was the salutary cessation of infections, but the abundant rainfall through the winter may set the stage for an additional substantial increase in cases during the customary summer and fall endemic season. This is based on the observations of Smith and co-workers[11] that following a heavy winter's rainfall a proportionate increase in cases of coccidioidomycosis can be expected in the summer-fall season. Physicians should be alert to this when encountering febrile respiratory illnesses.

With respect to diagnosis, many of the dust storm-related cases of coccidioidomycosis conformed to the expected clinical features: fever, pleuritic chest pain, malaise, myalgia and arthralgia. Erythema nodosum was observed in many patients. The resemblance of coccidioidomycosis to other febrile respiratory illnesses led to a delay in diagnosis of several cases in which there was persistence of malaise and low grade fever for four months or more. However, once again the unusual characterized some of the cases of coccidioidomycosis beclouding the diagnosis. This was the case, for example, in a woman in Sacramento in whom in the early stages of disease (in January) tenderness in the neck developed, the result of suppurative coccidioidal thyroiditis.

Recognizable extrapulmonary spread (dissemination) occurred relatively early after onset of the primary infections. Therefore, of the 379 dust storm-related primary infections recognized through our UCD studies during the first 12 weeks of 1978, in 16 (4.2 percent) recognizable dissemination developed. In 9 of these 16 (2.4 percent of the primary infections) meningitis developed. Most disseminations occurred in one to two months, fewer at two to three months, one at four months after onset of illness. Some few additional disseminations can be anticipated later. Some fatalities were associated with these coccidioidal infections, including four deaths from meningitis, two in Kern County; however, the precise numbers are not yet available. There was an apparent difference in age of patients infected during the dust storm in Kern County and those infected from the fallout north of Kern County in that the latter were virtually all adults whereas a large proportion of Kern County patients were under 12 years of age. The latter group released from school during the great turbulence apparently spent more time out of doors than the adults of Kern County who ensconced themselves indoors during the dust storm. Furthermore, a sizable proportion of adults of Kern County have already had their coccidioidal contact. (It is possible that pediatricians in northern California did not pursue the serologic or culture diagnosis of coccidioidomycosis as vigorously as did the physicians with adult patients.) The proportion of asymptomatic infections has not and probably could not now be determined in view of the lack of baseline studies. T. Larwood and co-workers, however, carried out skin tests in school children in Kern County four months after the dust storm and found a decrease in coccidioidin reactivity from that which they had previously determined in 1964 (T. Larwood—personal communication).

In a few instances biopsy studies yielded the diagnosis promptly by histopathologic means. In most of the other cases, serologic confirmation supported the diagnosis. The serologic studies showed once again the usefulness, indeed the necessity, of testing for the early precipitin type antibody.[13] This antibody precedes development of the complement fixing (CF) antibody by several days to weeks and may provide the only clue to early, primary acute coccidioidomycosis. This early antibody can be detected by the original tube precipitin text (used by very few laboratories), by the commercial coccidioidal latex particle agglutination, or by agar gel immunodiffusion provided the serum has been concentrated to enhance detection of the precipitins. Nevertheless, the CF test should also be carried out because the precipitins are relatively transient, and particularly if the diagnosis is delayed. While *conversion* of the skin test reactivity to coccidioidin or spherulin may itself be an early clue, a positive skin test finding per se can only suggest further diagnostic studies.

The problem of appropriate and effective therapy is still with us. Treatment of primary acute

coccidioidomycosis with the hope of forestalling dissemination has not been evaluated. The toxicity of and difficulty in administering amphotericin B has usually prompted reserving it for frankly disseminated cases or those with serious threat of dissemination. However, in these cases it remains the agent of first choice. Miconazole, the effectiveness of which is unequivocal only in some cases, also is difficult to administer.[15] The water soluble methyl ester of amphotericin B while apparently less toxic than the parent polyene[2] must also be given intravenously and its efficacy in man has not yet been fully assessed. The advent of two compounds—ketoconazole, an imidazole (Janssen Pharmaceuticals), and ambruticin (Warner-Lambert)[5]—that are effective when given by mouth in murine coccidioidomycosis gives some hope that perhaps humans may be treated early, before coccidioidal infections have disseminated. It should be recalled, however, that even amphotericin B was effective when given by mouth in mice infected with C. immitis,[14] so much work remains to determine if these newer compounds will be effective when given by mouth in man.

However, what remains a challenge is the cases of coccidioidomycosis that disseminate without an obvious or typical primary acute coccidioidal infection. Prevention of coccidioidomycosis through immunization offers promise.[4,6]

The challenge of all forms of coccidioidomycosis continues with an anticipated greater problem than usual confronting us with the advent of the 1978 summer and fall months. Such awareness must extend to physicians outside the endemic areas of the southwest as even those transiently present in these areas may return to other states and countries in which coccidioidomycosis is not the familiar word that it is in California.

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CONSULTANTS FOR

The Western Journal of Medicine in 1978

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in memoriam

Bachman, Kenneth P., La Mesa. Died February 27, 1978 of arteriosclerosis, aged 59. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1943. Licensed in California in 1958. Dr. Bachman was a retired member of the San Diego County Medical Society.

Clark, Edward C., San Francisco. Died October 12, 1978 at his home in Muir Beach, aged 60. Graduate of Western Reserve University School of Medicine, Cleveland, 1943. Licensed in California in 1952. Dr. Clark was a member of the San Francisco Medical Society.

Fishback, Hamilton R., Berkeley. Died October 5, 1978, aged 88. Graduate of Jefferson Medical College of Thomas Jefferson University, Philadelphia, 1916. Licensed in California in 1947. Dr. Fishback was a retired member of the Alameda-Contra Costa Medical Association.

Gale, Lester S., Bakersfield. Died October 15, 1978 in Los Angeles of renal failure, aged 70. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1937. Licensed in California in 1938. Dr. Gale was a member of the Kern County Medical Society.

Goldsand, Julius, San Francisco. Died August 2, 1978 in San Francisco, aged 79. Graduate of Marquette University School of Medicine, Milwaukee, 1928. Licensed in California in 1928. Dr. Goldsand was a member of the San Francisco Medical Society.

Guthrie, Joseph A., Greenbrae. Died September 13, 1978 in San Rafael, aged 60. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1942. Licensed in California in 1943. Dr. Guthrie was a member of the Marin Medical Society.

Helsley, Gordon F., San Jose. Died October 22, 1978, aged 89. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1918. Licensed in California in 1918. Dr. Helsley was a retired member of the Santa Clara County Medical Society.

Jackson, Frederick E., Fallbrook. Died October 14, 1978 in a light plane crash in Yucca Valley in San Bernardino County, aged 50. Graduate of Boston University School of Medicine, 1954. Licensed in California in 1956. Dr. Jackson was a member of the San Diego County Medical Society.

Johnson, Linares Bert, Edgemont. Died October 16, 1978 of injuries received in an automobile accident, aged 53. Graduate of the University of Michigan Medical School, Ann Arbor, 1958. Licensed in California in 1960. Dr. Johnson was an applicant for membership of the Riverside County Medical Association.

Kanner, Harry H., Sacramento. Died October 1, 1978 in Sacramento, aged 56. Graduate of Jefferson Medical College of Thomas Jefferson University, Philadelphia, 1950. Licensed in California in 1951. Dr. Kanner was a member of the Sacramento County Medical Society.

Levin, Herman G., Westwood. Died September 12, 1978 in Westwood, aged 73. Graduate of the University of Illinois College of Medicine, Chicago, 1929. Licensed in California in 1929. Dr. Levin was a member of the Lassen-Plumas-Modoc-Sierra County Medical Society.

Lirette, William L., Fresno. Died October 15, 1978, aged 45. Graduate of the University of Texas Medical Branch, Galveston, 1957. Licensed in California in 1973. Dr. Lirette was a member of the Fresno-Madera Medical Society.

McGiff, John J., Hayward. Died October 22, 1978 in Pleasanton of heart disease, aged 56. Graduate of Georgetown University School of Medicine, Washington, DC, 1952. Licensed in California in 1954. Dr. McGiff was a member of the Alameda-Contra Costa Medical Association.

Morreale, John J., Eagle Rock. Died September 18, 1978 while vacationing in the state of Washington, aged 63. Graduate of the University of Southern California School of Medicine, Los Angeles, 1940. Licensed in California in 1940. Dr. Morreale was a retired member of the Los Angeles County Medical Association.

Pearson, J. Kirk, Santa Monica. Died September 21, 1978, aged 75. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1941. Licensed in California in 1941. Dr. Pearson was a member of the Los Angeles County Medical Association.

Punta, Robert F., La Mesa. Died March 1, 1978, aged 52. Graduate of Northwestern University School of Medicine, Chicago, 1950. Licensed in California in 1954. Dr. Punta was a member of the San Diego County Medical Society.

Rose, Elise Meyer, San Francisco. Died October 9, 1978, aged 76. Graduate of the University of California Medical School, Berkeley-San Francisco, 1940. Licensed in California in 1940. Dr. Rose was a retired member of the San Francisco Medical Society.

Shofner, Jeffrey C., Los Altos. Died October 15, 1978 in Mountain View, aged 36. Graduate of the University of Michigan Medical School, Ann Arbor, 1969. Licensed in California in 1970. Dr. Shofner was a member of the Santa Clara County Medical Society.

Trask, Victor Myron, San Diego. Died November 25, 1977, aged 76. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1930. Licensed in California in 1930. MD degree from California College of Medicine, 1962. Dr. Trask was a retired member of the Orange County Medical Association.

BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

MALIGNANT MELANOMA OF THE SKIN AND MUCOUS MEMBRANE—G. W. Milton, MBBS(Adel), FRCS, FRACS, Professor of Surgery, University of Sydney, Director of the Melanoma Unit, Sydney Hospital, Honorary Surgeon, Sydney Hospital; Visiting Professor in Surgery, Liverpool District Hospital; With chapters by V. J. McGovern, MD(NZ), FRACP, FRCPath, FRCPA, Director, Fairfax Institute of Pathology, Royal Prince Alfred Hospital; Lecturer in Pathology, University of Sydney; and Martin G. Lewis, MD, MRC, Path(London), Director, Cancer Research Unit, McIntyre Medical Sciences Building, Montreal, with the assistance of Geoffrey Rowden and Terrence M. Phillips, McGill University Cancer Research Unit, McIntyre Medical Sciences Building, Montreal. Churchill Livingstone—Medical Division of Longman Inc., 19 West 44th St., New York City (10036), 1977. 174 pages, $29.00

This is a timely book, relating in great detail the authors' experiences with malignant melanoma at the Melanoma Unit in the Sydney Hospital, the University of Sydney, and the Queensland Melanoma Project in Australia, as well as the McGill University Cancer Research Unit in Canada. Nowhere in the world is the incidence of melanoma any higher than in the patient population observed by the authors, and their report and extensive review of the literature should command great respect.

The book is largely based on the authors' personal experience. The first chapter, on the etiology and pathology of melanoma, written by Dr. V. J. McGovern—whose extensive experience with melanoma is internationally recognized—includes a very complete and concise up-to-date review of the pertinent world literature on the subject. Dr. McGovern interprets the currently available information and adds his own personal experience. Of interest is his view that "most melanomas develop in pre-existent naevi." The published experience in the United States somewhat disputes this concept and advocates that melanomas arise any place where there are melanocytic cells, including nevi. Dr. McGovern proposes that melanomas commencing in nevi usually represent superficial spreading type of melanomas, which in turn are the most common form of the disease.

Possible etiologic factors in melanoma, including the relationship to sunlight, host susceptibility, familial and hormonal aspects, as well as other recently proposed contributing conditions, are discussed.

The importance of histologic grading of melanoma is emphasized, based on three grades of mitotic activity, as proposed by the International Group of Pathologists. Emphasis is also placed on the proper correlation of the microscopic and clinical data, including level of invasion, thickness (as proposed by Breslow), mitotic activity (nuclear grading), cellular response, sex, age and other known factors.

The chapters on clinical and differential diagnosis, biopsy, and treatment reflect Dr. Milton's experience. They tend to be repetitious, but well discussed, presenting many very fine details and clues not generally mentioned elsewhere in the literature. Unfortunately, the clinical photographic pictures appear too small, and the legends too long. In addition, they are arranged in a manner that somewhat detracts from the otherwise excellent presentation. His approach to biopsy and surgical treatment is dictated by logic and common sense. He supports the concept that a partial biopsy may not increase the risk of spread, and outlines indications or guidelines for partial incisional biopsies. The very fine and detailed descriptions of definitive therapeutic surgical procedures for the various forms and locations of melanomas should be of interest to all surgeons treating this disease. Accounts of many years of personal experience in the surgical management of melanoma, and critical analysis of published procedures, will be welcomed reading by anyone involved in its management, or personally confronted with this diagnosis. Besides describing the surgical procedure of choice in their hands, the preoperative and postoperative management, and the surgical complications are discussed, devoting complete chapters to problem areas, according to the location of the lesion. The survival data presented are meaningful but somewhat confusing.

The chapters dealing with spontaneous regression, metastases and management of metastases should be regarded as classics. The author also relates his own experiences with control of pain, chemotherapy, isolated limb perfusion, intralesional and topical chemotherapy, immunotherapy and radiotherapy. Very interesting discussions include those on melanoma in pregnancy and in children, and on occult primary tumors.

One of the strongest points of the book pertains to the detailed accounts of the authors' approach for informing patients and their families about the diagnosis of melanoma, and the subsequent relationships with them. Anyone engaged in medical practice will gain from this, and the patient handouts concerning the subject offer deep, meaningful insight that can be adapted for use by any melanoma or cancer unit anywhere.

The chapter on immunology and immunotherapy by Martin G. Lewis is also a most complete and up-to-date review, reflecting considerable clinical and research experience on the subject. Again, the figures and charts are somewhat confusing, but the discussion is clear and impartially presented. The final conclusions at the end of the chapter, concerning the state of the art pertaining to immunotherapy, appear very logical and offer some valuable guidelines to nonimmunologists managing melanoma.

The final chapter, on the care of the melanoma patient and of the dying, emphasizes a comprehensive, insightful and very humane approach to this very painful and sad disease. This chapter is recommended to all persons, medical and nonmedical, dealing with melanoma. In particular, the book has many sections that appear highly valuable for relatives of patients, and even for certain patients themselves.

Weaknesses of the book include a considerable amount of repetition, shortcomings of some clinical pictures and confusing tables. The authors did not significantly discuss acral lentiginous, genital, eye or amelonotic melanomas nor other variants such as spindle cell, desmoplastic or balloon cell melanomas.

The book is especially recommended for its discussions on occult primary melanomas, mechanisms of spontaneous regression, immunology, metastases, and for its warm, humanistic approach to the problem of melanoma. It is based on common sense and extensive experience, deserving of the highest recognition.

D. A. LOPEZ, MD
Assistant Professor of Medicine (Dermatology)
University of California, San Diego
Assistant Chairman
Director of Training and Head, Dermal Pathology
Department of Dermatology
Naval Regional Medical Center
San Diego

THE MAKING OF A MEDICARE DOCTOR—John M. Lanham, MD. Vantage Press, Inc., 516 West 34th Street, New York, NY (10001), 1977. 88 pages, $5.95.

This well-written little book expresses the views and frustrations of many if not most idealistic and conscientious physicians in America—perhaps particularly in rural America—today. It comes through rather as a protest against the way things are going than as a definitive contribution to solving any of the problems. One senses the author has found a zestful personal solution, and that writing this entertaining account of some of his personal experiences and observations was also therapeutic. The physician reader who has been out in practice for a while will find much with which to empathize in this little book and it may make him feel a little better, too. It did this reviewer.

MALCOLM S. M. WATTS, MD
San Francisco

* * *

CHILD CARE IN GENERAL PRACTICE—Edited by Cyril Hart, MA, MB, DLitt, MRCGP, General Practitioner, Yaxley, Peterborough. Churchill Livingstone—Medical Division of Longman, Inc., 19 West 44th St., New York City (10036), 1977. 442 pages, $16.00 (softbound).

In the British National Health Service all primary care of sick children is provided by general practitioners. Well-child care is provided occasionally by general practitioners, but mostly in Welfare (Public Health) Clinics. The 400 pediatricians in the country are hospital-based and see only sick children referred to them. Most general practitioners do not have hospital privileges. In the reorganization of the National Health Service in 1975 primary care teams consisting of general practitioners, public health and visiting nurses, and social workers are intended to be established, but this is not yet frequently seen and in the instances where the concept is in operation each member seems to practice individually rather than as part of a team. Therefore, one of the biggest problems in primary care in Britain is that preventive pediatrics, developmental surveillance and the care of sick children is fragmented and uncoordinated, and health education is rudimentary.

Child care represents about a fourth of a general practitioner's work load and as he is the sole provider of primary care for sick children in the National Health Service it is appropriate that a practical manual on child care in general practice should be written by general practitioners. Of the 32 contributors to the book, 29 are general practitioners. The book is intended to supplement the standard pediatric textbooks and to emphasize the childhood diseases commonly encountered in general practice. Therefore it was disappointing to find that such common problems as obesity, learning disorders and behavioral problems in children received rather cursory and simplistic consideration with little practical help provided for the physician of first contact. Developmental screening was also dealt with on a philosophical rather than practical level and the important work of Starte is glossed over in one paragraph. If, as is stated in the preface, the intent is to produce a practical manual for workers in the field of primary child care then a practical approach to coping with these common problems would seem to be a necessary part of the manual. Similar criticisms apply to the discussions on breast-feeding and artificial feeding, and the eye is virtually ignored, yet 50 percent of children in Britain with a squint at age 7 years have not been seen by any ophthalmologist. Allergic problems other than asthma remain either unrecognized or nonexistent in the United Kingdom, compared with the 15 percent of pediatric contacts in America.

The initial seven chapters on the organization of child care in Britain provide a wealth of information for students of the National Health Service and incidentally show that even after 30 years of the National Health Service the infant mortality rate is not falling as rapidly as in other European countries and that for older children there remains a steep social class gradient in mortality rates. The chapter "The Social Services and the Practice" defines very clearly the lack of equality among members of the primary care team but avoids the issue of how to achieve a team effort.

The sections on clinical care in acute illness, continuity care and essays in family care contain many well-written chapters. It is interesting to note that throat cultures do not play a part in the management of tonsillitis and that the time-wasting procedure of tickling the pharynx with a finger (ouch!) or spoon to induce vomiting in a child is still recommended. In the chapter "Care of the Newborn" a short period of asphyxia is considered almost inevitable at birth and represents a rather dangerous approach, particularly when carbohydrate metabolism rather than oxygen is defined as the means of coping with this.

The editor, Dr. Cyril Hart, and his contributors deserve to be congratulated on developing this manual which will be of great value to British general practitioners. For American family physicians the book represents an interesting comparison between entirely different methods and standards of child care.

DAVID M. E. ALLAN, MB, BChir, FAAP
Associate Dean
University of California, San Diego
School of Medicine
La Jolla, California

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108TH ANNUAL SESSION CALIFORNIA MEDICAL ASSOCIATION

LOS ANGELES BONAVENTURE • FIFTH & FIGUEROA

Friday, March 9

Eight scientific and educational sessions include: Seminars in Family Medicine; Anesthesia and the Cardiac Surgical Patient; Dying; Clinical Pediatrics; Adolescent Medicine; Stroke, and Clinical Obstetrics and Gynecology. The California Society of Internal Medicine cosponsors a 2-day program (Friday and Saturday) on socioeconomic, as well as clinical, topics relating to internists.

Saturday, March 10

A full schedule of outstanding conferences is slated. Among the topics are: Is There Life After Medical School, Asthma 1979, Iatrogenic Drugs, Imaging Modalities and Techniques, Rational Blood Infusion Therapy, Thyroid Cancer, The Paralyzed Face and Current Topics in Public Health and Psychiatry. The House of Delegates and exhibits open.

Sunday, March 11

Offers a choice of ten programs—Acute and Chronic Pain Control, Diagnosis and Management of Myofascial Pain, Update on Psychiatry, New Ideas in Urology and Related Matters, Expanding Dimensions in Plastic Surgery, Glaucoma Update, Drug Abuse: Distorter of Disease, Malignant Melanoma, Update on Coma and Diagnosis and Management of Seizure Disorder.

Monday, March 12

Social problems are addressed at courses on VD, abortion, holistic and humanistic medicine and impairment among physicians. Nuclear Medicine and Chest Diseases present a session on venous thrombosis and pulmonary embolism. Other programs on the agenda are CME Accreditation in California, Government and Medicine, and a Q&A session called "Dialogue." House of Delegates reconvenes. Auxiliary Convention begins.

Tuesday & Wednesday

House of Delegates continues.

Information

Plan to visit the exhibits and the CMA Service Center Exhibition Hall • 9 a.m. to 5 p.m. • Saturday-Monday

General registration—Exhibition Hall Lobby 7:30 a.m. to 5 p.m. • Friday-Monday

All scientific and educational programs are acceptable for Category I Credit in the CMA Certification Program

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MARCH 9-14, 1979 LOS ANGELES

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